REMARKS

I. Background

The claimed invention of the present application is directed to chemotherapeutic medicaments or pharmaceutical compositions for chemotherapeutic treatment that have a halogenated xanthene as the active component. For the reasons stated in Amendment A, filed May 7, 2003, as well as those presented infra, Applicants respectfully submit that no prior art anticipates nor renders obvious the claimed invention, as delineated by the amended set of claims provided herein. Accordingly, each of the Examiner's rejections in the Final Rejection are traversed herein as explained in depth infra.

First, however, Applicants believe that it will be beneficial to examine the claimed subject matter in order to compare this with the teachings in Goers, Bottiroli, and Schultz.

The pending, amended independent claims of the present invention are directed to chemotherapeutic medicaments or pharmaceutical compositions for chemotherapeutic treatment, wherein the sole active component is a halogenated xanthene. In order to make this clear, Applicants have amended the independent claims to recite a medicament or pharmaceutical composition *consisting of a halogenated xanthene* as the active component.

Further, the language of the independent claims makes it clear to one of ordinary skill in the art that the claimed chemotherapeutic medicaments and pharmaceutical compositions are drugs that control or cure disease by virtue of their intrinsic pharmacologic properties. Although they *could* be used in combination with other drugs or forms of therapy, such medicaments *do not require* such combination. Thus, by definition, these chemotherapeutic agents are capable of affecting their desired therapeutic effect without concurrent, prior, or *post factum* input of secondary agents,

energies, or other types of therapies. These important features would be clearly understood by the skilled practitioner based on the definition of a chemotherapy and the requisite chemotherapeutic medicaments used to affect such chemotherapy.

The clarity of the terms chemotherapy and chemotherapeutic medicaments is elucidated by a number of references. For example, the internet website for the *American Cancer Society* defines chemotherapy as follows:

> "The word chemotherapy was once used to mean any medicine for treating any disease. Even taking an aspirin would be chemotherapy. These days, chemotherapy is most often used to mean taking medicines, or drugs, to treat cancer. You might take these drugs before or after surgery, with radiation (x-ray) treatment, or you might take the drugs by themselves." (from *American Cancer Society* website, "Chemotherapy: What it is, how it helps" page)

> "To doctors, nurses, pharmacists, and health professionals, the word *chemotherapy* means any drug (such as aspirin or penicillin) used for treating people with any disease. Most of us, however, think of anticancer medicines to treat cancer when we hear the term *chemotherapy*. Two other medical terms often used to describe cancer chemotherapy are *antineoplastic* (meaning anticancer) and *cytotoxic* (cell-killing)." (from *American Cancer Society* website, "What is Chemotherapy?" page, emphasis in original; see Attachment A)

Thus, *chemotherapy* is the use of *chemotherapeutic medicaments* for treatment of disease, and more commonly for treatment of cancer. As the above passages indicate, typically such chemotherapeutic medicaments control or kill diseased tissue and are capable of functioning "by themselves."

Another reference (the *webMD* internet website) reiterates the intrinsic therapeutic function of chemotherapeutic medicaments:

> "Chemotherapy [refers] to medicine used to kill cancer. Doctors use a variety of terms to describe how "chemo," as it is more commonly called, is given, and include the following:
>
> "Adjuvant: This term is used when chemotherapy is given after the cancer is removed. The first treatment, such as radiation or surgery, is supposed to kill or

eliminate the cancer, while the adjuvant chemo is used to kill any cancer cells that may have been missed, such as cells that may have moved to the lymph nodes, but are too small to notice.

"Neo-adjuvant: This term is used when chemotherapy is given before surgery. Chemo may be given prior to surgery in order to shrink the tumor so that the surgeon can completely remove the tumor with fewer complications.

"Primary chemotherapy: is used when colorectal cancer is advanced and has already spread to different parts of your body. In this situation, surgery doesn't help much to eliminate the cancer so your best bet is to be treated with chemotherapy." (from www.webMD.com; see Attachment B)

In these examples, the chemotherapeutic medicament is used to treat diseased tissue (i.e., cancer); this therapeutic function may be employed alone (i.e., primary chemotherapy), or in conjunction with other treatment modalities (i.e., adjuvant or neo-adjuvant chemotherapy).

Further insight into this terminology can be found in definitions provided by the Merriam-Webster OnLine dictionary:

"chemotherapy (noun): the use of chemical agents in the treatment or control of disease or mental illness"

"chemotherapeutic (adjective): of, relating to, or used in chemotherapy" (from www.m-w.com; see Attachment C)

Thus, Merriam-Webster makes it clear that chemotherapy is the use of agents that treat disease, and that the requisite chemotherapeutic medicaments are medicaments "of, relating to, or used in chemotherapy."

Finally, a standard textbook of medicine (Cecil Textbook of Medicine, 21st Edition, Goldman and Bennett, eds.) makes it clear that chemotherapy is one of several independent modalities used for treatment of disease, such as cancer:

"Therapeutic Modalities. There are four principal therapeutic modalities for cancer. [These are: Surgery; Radiation Therapy; Chemotherapy: and Biologic Therapy]"

"Chemotherapy is used (1) as a definitive treatment ...; (2) as a principal form of treatment ...; or (3) as an adjuvant to another modality...." (Cecil, *ibid*, p. 1031; see Attachment D)

Moreover, on the role of chemotherapeutic medicaments, Cecil makes it clear that these act directly upon diseased tissue:

"Ideally, anticancer drugs should eradicate cancer without harming normal tissues...." (Cecil, *ibid*, p. 1031)

"An important concept in cancer chemotherapy is that cellular killing with cytotoxic agents follows first-order kinetics...." (Cecil, *ibid*, p. 1063)

Thus, chemotherapeutic medicaments typically are cytotoxic agents that selectively destroy (or otherwise treat) diseased tissue; such medicaments may be used alone or in conjunction with other forms of therapy, but do not require such other forms of therapy nor additional input of other agents or activating energies.

The specification of the present application is clearly consistent with this prevailing terminology. For example, the Background of the Invention states the following:

"[0002] The present invention is related to certain chemotherapeutic medicaments and methods for treatment of human or animal tissue using chemotherapy.

"[0003] Chemotherapy was developed to treat cancer and other disease with the promise of limiting the invasiveness of the therapeutic intervention. Ideally in

> the practice of chemotherapy, chemical agents that afford selective toxicity to diseased or otherwise undesirable tissue are administered to a patient....
>
> "[0004] Therefore, it is an object of the present invention to provide new chemotherapeutic medicaments...."

These chemotherapeutic medicaments are subsequently described in the present application in, for example, the Summary of the Present Invention, as follows:

> "[0005] The present invention is directed to new chemotherapeutic medicaments ... wherein a primary active component of such medicaments is a halogenated xanthene or a halogenated xanthene derivative. In a preferred embodiment, the halogenated xanthene is Rose Bengal or a functional derivative of Rose Bengal. The halogenated xanthenes constitute a family of extremely useful agents that can be selectively delivered at high concentrations to certain tissues. Selective retention of such agents at high concentrations in the desired tissues results in decreased viability or death of such tissues (and hence provides a chemotherapeutic use of medicaments containing agents)."

Thus, the specification of the present application teaches that the halogenated xanthenes have utility as the active component in a chemotherapeutic medicament.

The claimed chemotherapeutic medicaments are further exemplified in the present application in, for example, the Detailed Description of the Presently Preferred Embodiments, as follows:

> "[0028] It is thus one preferred embodiment of the present invention that a chemotherapeutic medicament be produced that contains, as an active ingredient ... at least one halogenated xanthene."

Applicants have herein described chemotherapeutic medicaments that contain, as an active ingredient, at least one halogenated xanthene. The remainder of the specification contains additional description of this fundamental invention, along with data demonstrating reduction to practice.

In contrast, Goers, Bottiroli and Schultz fail to disclose any chemotherapeutic properties of the halogenated xanthenes and cannot, therefore, anticipate or render obvious the claimed invention, for the specific reasons set out below.

Applicants will now address each of the Examiner's rejections in the order in which they appear in the Final Rejection

II. Claims Rejections - 35 U.S.C. §102

A. Rejection over Goers et al.

The Examiner rejects Claims 1, 3-8, 19, 21-26 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Goers. This rejection is respectfully traversed for at least the reasons discussed below.

(1) The photosensitizer described in Goers is not a chemotherapeutic agent.

In the Final Rejection, the Examiner states that the teachings of Goers "clearly state that the photosensitizers, including in particular Rose Bengal ... are disclosed as being therapeutic agents (i.e. photosensitizers including Rose Bengal) independent of the antibody attachment." The Examiner goes on to state that "the photosensitizer [in Goers] is activated by a light source and its cytotoxic effect is mediated through the production of singlet oxygen, which results in toxicity to neighboring cells...."

Applicants agree with this characterization of the teachings in Goers. However, such photosensitizers are not chemotherapeutic agents (such as is claimed in Applicants' amended claims). Specifically, without the active application of an external energy source, the photosensitizers in Goers have no therapeutic function. Accordingly, they *cannot function by themselves*, as required by the aforementioned definitions of chemotherapeutic agents, and thus are

not chemotherapeutic agents or medicaments. Goers fails to ascribe any therapeutic function to the photosensitizers disclosed therein in the absence of light activation, and thus fails to disclose any chemotherapeutic property of such photosensitizers (including Rose Bengal), and therefore fails to disclose or suggest a chemotherapeutic medicament.

(2) The therapeutic agents in Goers require an additional targeting moiety; the claimed invention does not.

In the Final Rejection, the Examiner states that "Goers et al. teach that the antibody or antibody fragment of the antibody therapeutic conjugate functions to deliver the conjugate agent to the target site, i.e. the antibody merely functions as a *targeting moiety* ...." Applicants agree with this characterization of the teachings in Goers, and point out that, according to the teachings in Goers, such additional targeting is required to achieve the desired therapeutic function of the "antibody therapeutic conjugate." According to the Summary of the Invention in Goers,

> "According to the general method of the present invention, a therapeutic agent is covalently attached to an antibody or antibody fragment. The covalent attachment of the therapeutic agent is accomplished so that the resulting antibody conjugate retains the ability to bind antigen." (col. 6, lines 34-39)

Thus, Goers requires conjugate agents, comprising (a) a therapeutic moiety and (b) a targeting moiety.

In contrast to what is disclosed in Goers, the inventors of the present application have discovered that the halogenated xanthenes are therapeutically active without the requirement of conjugation to a separate targeting moiety, and that they exhibit intrinsic targeting. This is explained in the specification which also teaches that this intrinsic targeting may be modified upon conjugation of the halogenated xanthenes to targeting moieties. However, this additional perturbation is not

required, nor is it claimed in independent Claims 1, 19 and 31 (which do not bear Goers' requirement of conjugation). Thus, whereas the claimed invention and present application teaches that the halogenated xanthenes have chemotherapeutic potential without conjugation, Goers teaches that therapeutic agents require conjugation to achieve sufficient targeting to diseased tissue. Accordingly, Goers fails to anticipate the invention of the independent claims and the central teachings of the present application (and in fact, teaches away from the intrinsic targeting of the halogenated xanthenes, as is clearly taught in the present application).

(3) Goers does not disclose or suggest the amended independent claims.

In the Final Rejection, the Examiner states that "other agents, such as conjugate agents, may be present within the medicament, potentially as a 'secondary' active agent...." The independent claims, as herein amended, do not allow for inclusion of conjugate agents, such as those in Goers, as additional active agents. Specifically, each independent claim clearly delineates that the sole active component consists of a halogenated xanthene. The claimed halogenated xanthenes do not include conjugates. Accordingly, the agents in Goers (which are not chemotherapeutic agents, nor non-conjugated forms of any halogenated xanthene) are not encompassed within the independent claims of the present application.

Since the chemotherapeutic medicaments of the claimed invention require neither (a) application of an external energy source nor (b) conjugation to an antibody in order to function properly, and furthermore (c) do not allow for incorporation of 'secondary' active agents such as those taught by Goers, the teachings in Goers are contrary to those of the claimed invention and cannot, therefore anticipate nor render obvious such invention.

Therefore, for at least the above-stated reasons, the rejected claims are clearly not disclosed or suggested by Goers but are patentable thereover. Hence, it is respectfully requested that this rejection be withdrawn.

B. Rejection Over Bottiroli

The Examiner also rejects Claims 1-11, 19-27 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Bottiroli et al. This rejection is also respectfully traversed for at least the reasons discussed below.

(1) Bottiroli requires conjugate agents; the claimed invention does not.

As Applicants noted in their response to the first Office Action, Bottiroli requires the use of conjugate agents, as illustrated by the following passages from this reference:

> "Fluorogenic substrates in the present invention are *derivates of xanthenes ... containing quencher groups* such as for example the acetate, sulphate, phosphate, dibutyryl ester, galacto-pyranoside, glucoronide, acetamide-dioxyglucopyranoside groups, respectively *recognisable by the enzymes*: esterase, sulphatase, phosphatase, lipase, beta-galactosidase, beta-glucoronidase, and glucoso-aminidase. (p. 3, lines 22-27, emphasis added)

This passage makes it clear that the teachings in Bottiroli are *exclusively* concerned with conjugate agents, such as the cited example of Rose Bengal Acetate. Such conjugate agents are even more tightly defined as those containing quencher groups that are capable of being cleaved by specific enzymes (i.e, esterase, sulphatase, phosphatase, lipase, beta-galactosidase, beta-glucoronidase, and glucoso-aminidase).

In contrast, as described in detail supra viz-a-viz Goers, the independent claims of the present application, as herein amended, do not require nor include such conjugate agents. Specifically, each

independent claim clearly delineates that the sole active component consists of a halogenated xanthene. The claimed halogenated xanthenes do not include conjugates of halogenated xanthenes. Accordingly, the agents in Bottiroli are not encompassed within the independent claims of the present application.

(2) Bottiroli requires photosensitization; the claimed invention does not.

Insofar as Bottiroli discloses use of certain derivatives of Rose Bengal, this disclosure does not include any chemotherapeutic use of or chemotherapeutic medicaments of Rose Bengal or any derivative thereof. In fact, Bottiroli teaches away from the fundamental subject matter of the present application by requiring photoactivation of the conjugate agent. In fact, in experiments with Rose Bengal Acetate, Bottiroli reports that, in the absence of photoactivation (i.e., in the absence of irradiation with light), "no significant cell mortality" occurs (see p. 7, lines 16-20 in Bottiroli). Bottiroli thereby teaches away from the fundamental teachings of the claimed invention and the present application, which itself shows that desirable, selective cell mortality can be produced using chemotherapeutic agents consisting of, for example, Rose Bengal, without the requirement of additional light activation.

(3) Bottiroli fails to observe or predict any chemotherapeutic properties of Rose Bengal.

The fact that Bottiroli fails to observe or predict any chemotherapeutic properties of Rose Bengal (as evidenced, for example, by the data on cellular vitality at p. 7, lines 16-20 in Bottiroli, cited supra) illustrates the novelty of the claimed invention, which is supported by e.g. Figure 3 of the present application. Bottiroli's tests of cellular vitality were conducted at a concentration of $1x10^{-4}$ M Rose Bengal (i.e., 0.1 mg/mL). Applicants discovered, as shown in the data of Figure 3, that such concentration is at the threshold for onset of cytotoxicity for this compound. Bottiroli,

however, fails to observe or predict any chemotherapeutic properties of Rose Bengal (or any other halogenated xanthene), thereby completely missing their potential use as chemotherapeutic agents, and completely failing to disclose or suggest chemotherapeutic medicaments, as claimed in the present application.

Since the therapeutic agents of the claimed invention require neither (a) conjugation to an enzyme-cleavable quencher in order to function properly, nor (b) activation using light energy after delivery to their target tissue, the teachings in Bottiroli are contrary to those of the claimed invention and cannot, therefore anticipate such invention.

For at least the aforementioned reasons, Applicants respectfully submit that the rejected claims of the present application are clearly distinguishable and patentable over Bottiroli and should be allowed. Accordingly, it is requested that this rejection now be withdrawn.

C. Rejection Over Schultz

The Examiner also rejects claims 1, 3-6, 19, 21-24 and 31-33 under 35 U.S.C. §102(b) as being anticipated by Schultz et al. This rejection is also respectfully traversed for at least the following reasons.

(1) Schultz requires conjugate agents; the claimed invention does not.

Similar to that discussed supra with respect to Goers and Bottiroli, Schultz *requires the use of conjugate agents*, as illustrated by the abstract therein:

> "*Polypeptide compositions* are provided having a binding site specific for a particular target ligand and further *having an active functionality* proximate the binding site. The *active functionality may be a reporter molecule* .... Alternatively, the *active functionality may be a chemotherapeutic agent*, in which case the

polypeptide compositions are useful for therapeutic treatment of various diseased states." (emphasis added)

Thus, compositions in Schultz are conjugate compositions (containing either diagnostic or therapeutic agents, depending upon the type of "active functionality" attached to the polypeptide).

In contrast, as described in detail supra viz-a-viz Goers and Bottiroli, the independent claims of the present application, as herein amended, do not require nor include such conjugate agents. Specifically, each independent claim clearly delineates that the sole active component consists of a halogenated xanthene. The halogenated xanthenes do not include conjugates of halogenated xanthenes. Accordingly, the agents in Schultz are not encompassed within the independent claims of the present application. Since the invention of the independent claims is free of the limitations in Schultz, Schultz does not disclose or suggest, and cannot anticipate nor render obvious the claimed invention.

(2) Schultz does not teach a therapeutic use of Rose Bengal or any halogenated xanthene.

Schultz describes two separate categories of conjugated polypeptides, namely (a) diagnostic conjugate agents and (b) therapeutic conjugate agents. For example, Schultz states:

> "Novel polypeptides having binding sites capable of specifically binding a predetermined target ligand include at least one active functionality proximate the binding site.... *The active functionality may be a reporter molecule*, whereby the polypeptides will be *useful in detecting* the predetermined target ligand in a sample suspected of containing such ligand.... *Alternatively, the active functionality may be a chemotherapeutic agent*, whereby the polypeptide will be *useful in treating a diseased state* by site-specific drug delivery." (col. 4, line 58 - col. 5, line 6, emphasis added)

Thus, the reporter-molecule conjugate in Schultz is used for *diagnostics* (i.e., "detecting the predetermined target ligand in a sample") while the chemotherapeutic-molecule conjugate is used for *treatment*.

The respective identities of the two distinct classes are established by several passages therein, including the following:

> "*Reporter molecules* and compounds are selected to *provide a detectable signal .... Suitable reporter molecules include* chromogens (e.g., dyes and *fluorophores*)....
>
> "A wide variety of fluorescers may be employed either by themselves or in conjunction with quencher molecules. *Fluorescers of interest* fall into a variety of categories having certain primary functionalities. These primary functionalities *include ... xanthene....*
>
> "*Individual fluorescent compounds* which have functionalities for linking or which can be modified to incorporate such functionalities *include ... rose bengal....*" (col. 9, line 32 - col. 10, line 27, emphasis added in Schultz)

In this passage, Schultz teaches that the xanthenes comprise one of several classes of "fluorescers of interest," and Rose Bengal is listed as a specific *fluorescent compound* of interest. Thus, as noted by the Examiner's comments in the pending Office Action, Schulz teaches that xanthenes and Rose Bengal have a *diagnostic use* (i.e., as fluorescent diagnostic reporter molecules when conjugated to certain polypeptides).

Turning to Schultz's separate class of chemotherapeutic agents, the reference teaches the following:

> "Chemotherapeutic agents will be selected depending on the diseased state which is being treated as well as on the nature of the target ligand.... Exemplary chemotherapeutic agents include toxins, toxin fragments, bactericides, radical scavengers, radical generators, alkylating agents, neurotransmitters, radionuclides, antiviral compounds, antifungal compounds, antineoplastic agents, antimycoplasmal agents, heavy metals, and the like. A list of suitable drugs is provided in Table 1. (col. 11, lines 8-21)

In contrast to the aforementioned case for "reporter molecules," Schultz fails to include xanthenes or Rose Bengal in this list of chemotherapeutic agents (this is also the case for Table 1 in the reference). Accordingly, despite reference to certain diagnostic uses for Rose Bengal, Schultz fails

to disclose or suggest any therapeutic or chemotherapeutic role for Rose Bengal or any other halogenated xanthene and fails to disclose or suggest the claimed chemotherapeutic medicaments of the present application.

Therefore, for at least the above-stated reasons, it is respectfully submitted that Schultz fails to disclose or suggest the claimed invention, and that the claims of the present application are patentable thereover. Accordingly, it is requested that this rejection be withdrawn.

Therefore, for at least the above-stated reasons, it is respectfully requested that each of the §102 rejections be withdrawn.

II. Claim Rejections - 35 U.S.C. §103

The Examiner also rejects claims 2 and 20 under 35 U.S.C. §103(a) as being obvious over Goers et al. This rejection is also respectfully traversed for at least the following reasons.

(1) Goers requires conjugate agents; the claimed invention does not.

As discussed in detail supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of conjugate agents. In contrast, the claimed invention does not require such conjugation. For at least this reason, the teachings in Goers do not render the claimed invention obvious.

(2) Goers requires photosensitization; the claimed invention does not.

Also as discussed in detail supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of photosensitization with its conjugate agents. In contrast, the claimed invention does not require such photosensitization. For at least this reason, the teachings of Goers do not render the claimed invention obvious over Goers.

Since the therapeutic agents of the claimed invention require neither (a) conjugation to any targeting moiety in order to function properly, nor (b) activation using light energy applied after delivery to their target tissue, and since both such features are required by Goers, the teachings in Goers are contrary to those of the claimed invention and cannot, therefore make the invention in part or as a whole obvious.

Therefore, for at least the reasons discussed above, it is respectfully requested that the §103 rejection be withdrawn.

IV. Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this response, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: September 22, 2003

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Chemotherapy Principles

The thought of having chemotherapy frightens many people. Almost everyone has heard stories about someone who was "on chemo." But we believe that knowing what chemotherapy is, how it works, and what to expect can often help calm your fears and give you more of a sense of control.

- What Is Chemotherapy?
  Knowing what chemotherapy is, how it works, and what to expect can often help calm your fears and give you more of a sense of control...
- How Does Chemotherapy Work?
  To understand how chemotherapy works as a treatment, it is helpful to understand the normal life cycle of a cell in the body...
- What Are the Goals of Treatment With Chemotherapy?
  There are three main goals for chemotherapy treatment: Cure, control, and palliation...
- What Are the Different Types of Chemotherapy Drugs?
  Chemotherapy drugs are divided into several categories based on how they affect specific chemical substances within cancer cells...
- Selecting Which Drugs to Use for Chemotherapy Treatments
  Factors to consider in choosing which drugs to use for each patient's chemotherapy treatment or regimen...
- Planning Drug Doses and
- What Are the Different Ways To Take Chemotherapy?
  Drugs used in chemotherapy regimens can be given in many ways...
- Safety Precautions for Healthcare Professionals
  Chemotherapy drugs are considered hazardous, so the nurses and doctors who give chemotherapy will take precautions to avoid direct contact with the drugs while administering them...
- What Are the Side Effects of Chemotherapy?
  Side effects are different for each chemotherapy drug, and they also differ based on the dosage, the route the drug is given, and how the drug affects you individually...
- What Questions Should I Ask About Chemotherapy?
  You may want to ask your doctor or nurses the following questions about your treatment plan for chemotherapy...
- What's New in Chemotherapy Research?
  New drugs, new combinations of

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- Why sh register?

against cancer.
Donate and volunteer.
It's easy and fun!
- Learn more

Schedules
Some drugs, especially those available to people without a prescription have a relatively wide therapeutic index...

- Where Are Chemotherapy Treatments Given?
In addition to considering what is most convenient to you, it is important to consider how the drugs are to be given...

chemotherapy drugs, and new delivery techniques hold significant promise for curing or controlling cancer and improving the quality of life of people with cancer...

- Additional Resources
- References

Chemotherapy: What It Is, How It Helps

Introduction

The word chemotherapy was once used to mean any medicine for treating any disease. Even taking an aspirin would be chemotherapy. These days, chemotherapy is most often used to mean taking medicines, or drugs, to treat cancer. You might take these drugs before or after surgery, with radiation (x-ray) treatment, or you might take the drugs by themselves.

Cancer chemotherapy is not new. It has been helping people since the early 1950s. The chemotherapy drugs your doctor suggests have been tested again and again. Careful research shows they work. Partly because of chemotherapy, many people with cancer live full and happy lives.

How Chemotherapy Works

If your doctor wants you to have chemotherapy, it means something can be done to try to control, or even cure, your cancer.

Cancer is a group of cells that divide quickly and are growing out of control. The word cancer is just a broad name for many different diseases. They all affect your body in different ways. But these diseases have one thing in common, they involve cells growing out of control. Everyone's cancer is different, and so is the chemotherapy that is given.

You and your doctor will decide on what chemotherapy is best for your cancer. Together, you will plan a schedule that works for you.

How Is Chemotherapy Given?

Most chemotherapy drugs are given in one of the following ways:

- You might simply swallow a pill. If your chemotherapy is a pill, just swallow it as your doctor prescribes.
- Sometimes chemotherapy is given like a flu shot. The shots may be given in your doctor's office, a hospital, a clinic, or at home.
- Sometimes drugs are given right into your veins through a needle. This is called an IV (intravenous) injection.

You may take chemotherapy once a day, once a week, or even once a month, depending on the type of cancer you have and the chemotherapy

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you are taking. How long you take chemotherapy also depends on the type of cancer and what length of time research has shown produces the best treatment results.

How Much Does Chemotherapy Cost?

How much chemotherapy costs will depend on a lot of things, such as the kinds of drugs used and how often you take them. You can ask about the cost and where to get help in paying for chemotherapy if you need it. If you have medical insurance, check to see if it pays for chemotherapy. You may also want to ask a social worker at your local hospital to help you look into payment through government programs, such as Medicare and Medicaid, or other agencies.

What Are the Side Effects of Chemotherapy?

Some people have no side effects at all from chemotherapy. Sometimes, however, chemotherapy will make you feel sick. This is because the drugs being used are very strong. They go after any cell that is quickly dividing, whether it's a cancer cell or not. So, some non-cancer cells that divide quickly are also damaged.

Parts of the Body Affected by Chemotherapy

- Cells in your hair and bone marrow (can cause hair loss and a tired feeling)
- Cells of the skin and mouth (can cause sores in your mouth, and dry skin and hair)
- Cells in your stomach and intestines (can cause you to feel nauseated)

Bone marrow changes: Bone marrow, which makes your blood cells (red blood cells, white blood cells, and platelets) is often affected by chemotherapy in the following ways:

- It may not be able to make enough red blood cells. Not having enough red blood cells is called anemia and causes weakness and fatigue.
- White blood cells fight infection. Chemotherapy lowers your white blood cell count, which can lower your resistance to infections. Your cancer care team may recommend certain precautions to avoid infection, such as wearing a surgical mask, not being near people with colds, not eating uncooked foods, and washing your hands thoroughly.
- Platelets form blood clots that plug up any cuts or bruises. If your bone marrow cannot make enough platelets, you may bleed too much, even from small cuts. If your platelet count is very low, you will need to be very careful to avoid any cuts or bruises. Even brushing your teeth with a brush that has hard bristles could cause your gums to bleed, so you may need a special toothbrush.

Hair, skin, mouth, and stomach: Cells in your hair, skin, mouth and gastrointestinal tract (stomach and intestines) can be affected by chemotherapy. This can result in hair loss, sores in your mouth, dry skin, nausea, and vomiting.

Sexuality: Chemotherapy can affect sexuality in both men and women. Sometimes sexual desire is decreased for a period of time, then returns. Some drugs given during chemotherapy may affect a woman's hormones, triggering hot flashes and dryness of the vagina. For more information on

the sexual effect of chemotherapy, please see Sexuality & Cancer: For The Man Who Has Cancer & His Partner or Sexuality & Cancer: For The Woman Who Has Cancer & Her Partner.

The good news is that there are things you can do to lessen or to get rid of some of these side effects.

- You can take some medicines at the same time as your chemotherapy to prevent vomiting or feeling sick to your stomach.
- New drugs called growth factors can be given as injections to help the bone marrow recover from chemotherapy, and start making new blood cells.
- Transfusions of red blood cells or platelets from blood donors help many people.

Remember that not everyone gets the same chemotherapy drugs. Chemotherapy for some cancers may be much stronger and cause more side effects than other drugs. Also, everybody is different. Your general state of health and fitness will affect how your body reacts to chemotherapy.

You may be able to go on with what you normally do while you are on chemotherapy. You may not have to stop working or be on a special diet. On the other hand, some people need to be in the hospital so that doctors can watch them closely and treat certain side effects. Ask your cancer care team what you'll be able to do while you're being treated.

Chemotherapy and Possible Effects on Your Family

Cancer isn't contagious, so you can go on being close to family and friends. Having chemotherapy won't "rub off " on anybody else either. Depending on how your body reacts to the treatment drugs, people may not notice you are on chemotherapy at all. If you do get unpleasant side effects, your family and friends can do things to help. When someone asks, "How can I help?" have a few suggestions ready.

- You may not feel like eating very much, so ask family members to take turns cooking foods that you feel you can eat.
- You might get tired after each treatment and need extra rest. Ask your family to do little jobs for you until you feel better.

Remember that your family cares very much about you and they may feel nervous about your chemotherapy. Let your family and friends know how much their support means to you. Be honest about how you feel. Get into the habit of talking things over with your family and friends so they can share your ups and downs.

There will be times when the people closest to you also feel tired or sad, and you can help them feel better by reminding them how much you value their help.

You and Your Doctor

Because cancer is different for everyone, your chemotherapy will be planned just for you. Work closely with your doctor to decide what's best for you.

- **Ask questions:** Ask the doctor, nurses, social workers, and other professionals on your team as many questions as you like. They

know the most about chemotherapy and how it works.

- **Come prepared:** Write down your questions ahead of time and don't be afraid to say you are confused, or want to ask the same questions over again. Nothing you say will sound "silly" or "strange" to your health care team, because they know you want to understand chemotherapy as much as possible. All patients receiving chemotherapy have questions.

These are some questions you might want to ask:

- What are the usual side effects of the chemotherapy you recommended?
- Is there any way to make these side effects less severe?
- How long do the side effects last? Are any permanent?
- How will this chemotherapy affect my prognosis (outlook) for cure or long-term survival?

Additional Resources

Additional American Cancer Society Publications

- Chemotherapy Principles
- Understanding Chemotherapy: A Guide for Patients and Families

Revision date: 2/9/2001

What Is Chemotherapy?

To doctors, nurses, pharmacists, and health professionals, the word *chemotherapy* means any drug (such as aspirin or penicillin) used for treating people with any disease. Most of us, however, think of anticancer medicines to treat cancer when we hear the term *chemotherapy*. Two other medical terms often used to describe cancer chemotherapy are *antineoplastic* (meaning anticancer) and *cytotoxic* (cell-killing).

History of Chemotherapy

The first drug used for cancer chemotherapy was not originally intended for that purpose. Mustard gas was used as a chemical warfare agent during World War I and was studied further during World War II. During a military operation in World War II, a large number of military personnel were accidentally exposed to mustard gas and were later found to have abnormally low white blood cell counts. It was reasoned that an agent that damaged the rapidly growing white blood cells might have a similar effect on cancer. Therefore, in the 1940s, several patients with advanced lymphomas (cancers of certain white blood cells) were given the drug by vein, rather than by breathing the irritating gas. Their improvement, although temporary, was remarkable. That experience started researchers studying other substances that might have similar effects against cancer. As a result, many other drugs have been developed to treat many other types of cancer.

Why Chemotherapy Is Different from Other Treatments

Chemotherapy is sometimes the first choice for treating many cancers. It differs from surgery or radiation in that it is almost always used as a systemic treatment. This means the medicines travel throughout the whole body or system rather than being confined or localized to one area such as the breast, lung, or colon. This is important because chemotherapy can reach cancer cells that may have spread to other parts of the body.

More than 100 drugs are currently used for chemotherapy -- either alone or in combination. Many more are expected to become available. These chemotherapy medicines vary widely in their chemical composition, how they are taken, their usefulness in treating specific forms of cancer, and their side effects. New medications are first developed through laboratory research in test tubes and animals. Then, their safety and effectiveness are tested in 3 phases of clinical trials in humans.

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Chemotherapy in Clinical Trials

Clinical trials are studies of new or experimental medicines (or other new treatments). The studies are done when there is a reason to believe a new drug or a new combination of drugs may be of value in curing or controlling cancer.

If you wish to take part in a clinical trial, the researchers will fully explain to you and your family what is required. You always have the chance to refuse to take part in the study. Being in a clinical trial does not keep you from getting other medical or nursing care that you need.

People who take part in clinical trials make an important contribution to medical care because the study results will also help future patients. At the same time, they may also be among the first to benefit from these new treatments.

The American Cancer Society offers a clinical trials matching service for patients, their family, and friends. You can gain access to this service through the ACS cancer information center (1-800-ACS-2345) or our Web site (www.cancer.org) Based on the information you provide about your cancer type, stage, and previous treatments, our computer will compile a list of clinical trials that match your medical needs. In finding a center most convenient for you, the service can also take into account where you live and whether you are willing to travel.

You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll free at 1-800-4-CANCER or visiting the NCI clinical trials Web site www.cancer.gov/search/clinical_trials/.

What Are the Different Types of Chemotherapy Drugs?

Chemotherapy drugs are divided into several categories based on how they affect specific chemical substances within cancer cells, which cellular activities or processes the drug interferes with, and which specific phases of the cell cycle the drug affects. Knowing this helps oncologists decide which drugs are likely to work well together and, if more than one drug will be used, plan exactly when each of the drugs should be given (in which order and how often).

Alkylating Agents

Alkylating agents work directly on DNA to prevent the cancer cell from reproducing. As a class of drugs, these agents are not phase-specific (in other words, they work in all phases of the cell cycle). These drugs are active against chronic leukemias, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and certain cancers of the lung, breast, and ovary.

Examples of alkylating agents include busulfan, cisplatin, carboplatin, chlorambucil, cyclophosphamide, ifosfamide, dacarbazine (DTIC), mechlorethamine (nitrogen mustard), and melphalan.

Nitrosoureas

Nitrosoureas act in a similar way to alkylating agents. They interfere with enzymes that help repair DNA . These agents are able to travel to the brain so they are used to treat brain tumors as well as non-Hodgkin's lymphomas, multiple myeloma, and malignant melanoma.

Examples of nitrosoureas include carmustine (BCNU) and lomustine (CCNU).

Antimetabolites

Antimetabolites are a class of drugs that interfere with DNA and RNA growth. These agents work during the S phase and are used to treat chronic leukemias as well as tumors of the breast, ovary, and the gastrointestinal tract.

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Examples of antimetabolites include 5-fluorouracil, capecitabine, methotrexate, gemcitabine, cytarabine (ara-C), and fludarabine.

Antitumor Antibiotics

Antitumor antibiotics interfere with DNA by stopping enzymes and mitosis or altering the membranes that surround cells. (They are not the same as antibiotics used to treat infections.) These agents work in all phases of the cell cycle. Thus, they are widely used for a variety of cancers.

Examples of antitumor antibiotics include dactinomycin, daunorubicin, doxorubicin (Adriamycin), idarubicin, and mitoxantrone.

Mitotic Inhibitors

Mitotic inhibitors are plant alkaloids and other compounds derived from natural products. They can inhibit, or stop, mitosis or inhibit enzymes for making proteins needed for reproduction of the cell. These work during the M phase of the cell cycle.

Examples of mitotic inhibitors include paclitaxel, docetaxel, etoposide (VP-16), vinblastine, vincristine, and vinorelbine.

Corticosteroid Hormones

Steroids are natural hormones and hormone-like drugs that are useful in treating some types of cancer (lymphoma, leukemias, and multiple myeloma) as well as other illnesses. When these drugs are used to kill cancer cells or slow their growth, they are considered chemotherapy drugs. They are often combined with other types of chemotherapy drugs to increase their effectiveness.

Examples include prednisone and dexamethasone.

Sex Hormones

Sex hormones, or hormone-like drugs, alter the action or production of female or male hormones. They are used to slow the growth of breast, prostate, and endometrial (lining of the uterus) cancers, which normally grow in response to hormone levels in the body. These hormones do not work in the same ways as standard chemotherapy drugs.

Examples include anti-estrogens (tamoxifen, fulvestrant), aromatase inhibitors (anastrozole, letrozole), progestins (megestrol acetate), anti-androgens (bicalutamide, flutamide), and LHRH agonists (leuprolide, goserelin).

Immunotherapy

Some drugs are given to people with cancer to stimulate their immune systems to more effectively recognize and attack cancer cells. These drugs offer a unique method of treatment, and are often considered to be separate from "chemotherapy."

Others

Some chemotherapy drugs act in slightly different ways and do not fit into any of the other categories.

Examples include such drugs as L-asparaginase and tretinoin.

Making Treatment Decisions

What Are the Different Ways To Take Chemotherapy?

Drugs used in chemotherapy regimens can be given in many ways:

- Oral (by mouth or PO)
- Topical (on top of the skin as a cream or lotion)
- Intravenous (into a vein or IV)
- Intramuscular (into a muscle or IM)
- Subcutaneous (under the skin or SQ)
- Intra-arterial (into an artery)
- Intrathecal (into the central nervous system via the cerebrospinal fluid)
- Intrapleural (into the chest cavity)
- Intraperitoneal (into the abdominal cavity)
- Intravesical (into the bladder)
- Intralesional/intratumoral (into the tumor)

Some chemotherapy drugs are never taken by mouth because the digestive system cannot absorb them or because they are very irritating to the digestive system. Even when a drug is available in an oral form (such as a pill), this method may not be the best choice. For example, some people with certain digestive system symptoms (vomiting, diarrhea, or severe nausea) cannot swallow liquids or pills. Some people may have trouble remembering when or how many pills to take.

The term *parenteral* is used to describe drugs given intravenously, intramuscularly, or subcutaneously. The IV route is most common. Intramuscular and subcutaneous injections are less frequently used because many drugs can be very irritating or even damaging to the skin or muscle tissue.

The IV route gets the drug quickly throughout the body. IV therapy may be given through a vein in the arm or hand or through a vascular access device (VAD), which includes a catheter implanted into a larger vein in the chest, neck, or arm.

There are different types of VADs with different types of catheters and implantable ports. VADs are used for these reasons:

- To give several drugs at one time
- For long-term therapy (to reduce the number of needle sticks)
- For continuous infusion chemotherapy

- To give drugs that can cause serious damage to skin and muscle tissue if they leak outside of a vein (drugs that are vesicants). Delivering them through a VAD provides more stable access in a vein than a regular IV, thus reducing the risk of the drug leaking outside of the vein.

The type of VAD used is based on the length of chemotherapy planned, your preference and what your doctor may suggest, the care required to maintain the VAD, and its cost.

Types of Vascular Access Devices

Type of Device	Comments
PICC (peripherally inserted central catheter) (Per-Q-Cath, Groshong PICC)	Placed in the arm and threaded thro vein to up near the heart. Allows for continuous access to peripheral veir several weeks. No surgery needed. catheter needed.
Midline catheter (Per-Q-Cath Midline, Groshong Midline)	Also placed in the arm, but the cathe not inserted as far as a PICC. Used intermediate length therapy when a peripheral IV is not advisable or ava No surgery needed. Care of cathete needed.
TCVC (Tunneled Central Venous Catheter) (Hickman, Broviac, Groshong)	Catheter with multiple lumens surgic placed in large central vein in the ch catheter tunneled under the skin. Ca catheter needed.
Implantable Venous Access Port (Port-A-Cath, BardPort, PassPort, Medi-port)	A port of plastic, stainless steel, or ti with a silicone septum with catheter surgically placed under the skin of th or arm in a large or central vein. The accessed by a needle to give chemc
Implantable pump	A titanium pump with an internal pov source surgically implanted to give continuous infusion chemotherapy, home. There is a refillable reservoir continuous infusions.

Chemotherapy for Specific Areas of the Body (Regional Chemotherapy)

When there is a need to give high doses of chemotherapy to a specific area of the body, it may be given by a regional method. Regional chemotherapy involves directing the anticancer drugs into the tumor-bearing part of the body. The purpose is to achieve greater exposure to the cancer than could be achieved by chemotherapy drugs that go to all parts of the body, while minimizing side effects elsewhere. Examples of regional chemotherapy include drugs given into the body through these routes:

- Intra-arterial (into an artery)
- Intravesical (into the bladder)

- Intrapleural (into the chest)
- Intraperitoneal (into the abdomen)
- Intrathecal (into the central nervous system via spinal fluid)

Intra-arterial infusions gained some popularity during the 1980s. An intra-arterial infusion allows a chemotherapy drug to be given directly through a catheter in an artery to an organ such as the liver (isolated hepatic perfusion) or to an extremity such as the leg (isolated limb perfusion). The catheter is attached to an implanted or portable pump. Although this approach sounds like a good idea for increasing effectiveness and reducing side effects, most studies have not found it to be as useful as was anticipated. Although clinical trials continue to improve this approach to chemotherapy, it is not widely used except in these studies.

Intracavitary is a broad term used to describe chemotherapy given directly into a body cavity such as intravesical (into the bladder), intraperitoneal (abdominal cavity), or intrapleural (chest cavity) chemotherapy. The drug is given through a catheter placed directly into one of these areas.

Intravesical chemotherapy is especially effective for early stage bladder cancer. The chemotherapy is usually given weekly for 4 to 12 weeks. For each treatment ing a urinary catheter is placed into the bladder to give the drug. The drug is kept in the bladder for 2 hours and then drained. The urinary catheter is removed after each treatment.

Intrapleural and intraperitoneal chemotherapy are not used very often but are useful for some people with mesothelioma (cancer that develops in the lining of the lung), ovarian cancer that has spread to the peritoneum, and lung or breast cancers that have spread to the pleura.

Intrapleural chemotherapy is given through large or small chest catheters that may be connected to an implantable port. These catheters can be used to administer drugs as well as to drain fluid that often accumulates in the pleural or peritoneal cavity when cancer has spread to these tissues.

Intraperitoneal chemotherapy is given through a Tenckhoff catheter (a catheter specially designed for removing or adding large amounts of fluid from or into the peritoneum) or through an implanted port. Cancers of the appendix that spread extensively within the abdomen are sometimes treated with intraperitoneal chemotherapy.

Intrathecal chemotherapy is given directly into the cerebrospinal fluid (fluid that surrounds the brain and spinal cord) and can reach cancer cells in the central nervous system. Most chemotherapy drugs that are given into veins are unable to cross the barrier between the bloodstream and the central nervous system (brain and spinal cord) called the blood-brain barrier. Intrathecal chemotherapy may be necessary for some people with leukemia or other cancers that have spread to the brain or spinal cord.

Intrathecal chemotherapy may use one of 2 methods:

- In one method, chemotherapy is given by a lumbar puncture (spinal tap) daily or weekly into the space around the spinal cord.
- The second method uses a special device called an Ommaya reservoir, which is placed into the skull and has a catheter inserted into a ventricle (a space inside the brain filled with cerebrospinal fluid).
- Safety Precautions for Healthcare Professionals

Many chemotherapy drugs are considered hazardous, so the nurses and doctors who give chemotherapy will take precautions to avoid direct contact with the drugs while giving them to you.

Some chemotherapy drugs are dangerous to others in these ways:

- They can cause abnormal changes in DNA (mutagenic).
- They may be able to alter development of a fetus or embryo, leading to birth defects (teratogenic).
- They may be able to cause another type of cancer (carcinogenic).
- Some may cause localized skin irritation or damage.

Nurses may wear special gloves and gowns when preparing and giving you the chemotherapy drugs. Additionally, pharmacists or nurses prepare the drugs in areas with special ventilation systems.

If you are hospitalized, nurses and health care professionals may take special precautions in handling your urine and stool for a few days after treatment, as they may contain the drugs. If you are receiving chemotherapy drugs at home, you will be given special instructions and precautions to ensure the safety of caregivers in the home.

Special procedures are used for disposing of materials after mixing and administering the drugs. There are separate plastic containers to dispose of sharp items, syringes, IV tubing, and medication bags. Gowns and gloves are disposed of in special bags. If any drug leaks or spills, special precautions are used to clean up the drugs.

Chemotherapy

What Is Chemotherapy?

Chemotherapy is just a fancy word cancer specialists use to refer to medicine used to kill cancer. Doctors use a variety of terms to describe how "chemo," as it is more commonly called, is given, and include the following:

Adjuvant: This term is used when chemotherapy is given after the cancer is removed. The first treatment, such as radiation or surgery, is supposed to kill or eliminate the cancer, while the adjuvant chemo is used to kill any cancer cells that may have been missed, such as cells that may have moved to the lymph nodes, but are too small to notice.

Neo-adjuvant: This term is used when chemotherapy is given before surgery. Chemo may be given prior to surgery in order to shrink the tumor so that the surgeon can completely remove the tumor with fewer complications.

Primary chemotherapy: is used when colorectal cancer is advanced and has already spread to different parts of your body. In this situation, surgery doesn't help much to eliminate the cancer so your best bet is to be treated with chemotherapy.

Talk to your doctor to determine the best treatment strategy for you.

How Is Chemotherapy Given?

Generally, chemotherapy is administered into a vein or, rarely, by mouth and will affect cancer cells anywhere in the body. Occasionally, chemotherapy can be administered regionally (through an artery) to target an isolated tumor. Regional chemotherapy is uncommon and can only be done in highly selected circumstances.

What are the Side Effects of Chemotherapy?

guide
- Get the Facts
- Risk Factors
- Prevention
- Tests You Take
- Your Treatment Options
- Follow-up
- Day-to-Day
- Caregiving

- To the Colorectal Cancer Center

Because the mechanism of chemotherapy is to kill rapidly dividing cancer cells, it also kills other rapidly dividing healthy cells in our bodies, such as the membranes lining the mouth, the lining of the gastrointestinal tract, the hair follicles, and the bone marrow. As a result, the side effects of chemotherapy relate to these areas of damaged cells.

The side effects of chemotherapy include nausea, vomiting, loss of appetite, hair loss, mouth sores, hand and foot rash, and diarrhea. Other side effects associated with chemotherapy's effects on the bone marrow include an increased risk of infection (due to low white blood cell counts), bleeding or bruising from minor injuries (due to low blood platelet counts), and anemia related fatigue (due to low red blood cell counts).

The side effects of chemotherapy depend upon the drugs given and the individual. For example, hair loss is not common in most chemotherapy currently offered for colorectal cancer. However, some people may experience some hair thinning. Although it may take some time, side effects related to chemotherapy will resolve when chemotherapy is stopped.

If you are experiencing any side effects, tell your doctor. In many cases, such as for nausea and vomiting, there are medications available to control side effects.

Next: Radiation >

Dec. 2001, Medically Reviewed by Gary Vogin, MD, WebMD.

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Main Entry: **che·mo·ther·a·py**
Pronunciation: -'ther-&-pE
Function: *noun*
Etymology: International Scientific Vocabulary
Date: 1910
: the use of chemical agents in the treatment or control of disease or mental illness
- **che·mo·ther·a·pist** /-pist/ *noun*

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\ə\ as **e** in kitten	\E\ as **ea** in easy	\oi\ as **oy** in boy
\&r\as **ur/er** in further	\g\ as **g** in go	\th\ as **th** in thin

\a\ as **a** in ash
\A\ as **a** in ace
\ä\ as **o** in mop
\au\ as **ou** in out
\ch\ as **ch** in chin
\i\ as **i** in hit
\I\ as **i** in ice
\j\ as **j** in job
\[ng]\ as **ng** in sing
\O\ as **o** in go
\th\ as **th** in the
\ü\ as **oo** in loot
\u\ as **oo** in foot
\y\ as **y** in yet
\zh\ as **si** in vision

For more information see the Guide To Pronunciation.

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Main Entry: **che·mo·ther·a·peu·tic**
Pronunciation: -"ther-&-'pyü-tik
Function: *adjective*
Date: 1907
: of, relating to, or used in chemotherapy
- **chemotherapeutic** *noun*
- **che·mo·ther·a·peu·ti·cal·ly** /-ti-k(&-)lE/ *adverb*

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For more information see the Guide To Pronunciation.

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TEXTBOOK of MEDICINE

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PART XIV

ONCOLOGY

189 INTRODUCTION

Joseph V. Simone

BACKGROUND

DEFINITIONS, INCIDENCE, AND MORTALITY. Cancer describes a class of diseases characterized by the uncontrolled growth of aberrant cells. Cancers kill by the destructive invasion of normal organs through direct extension and spread to distant sites through the blood, lymph, or serosal surfaces. The abnormal clinical behavior of cancer cells is often mirrored by biologic aberrations such as genetic mutations, chromosomal translocations, expression of fetal or other discordant ontologic characteristics, and the inappropriate secretion of hormones or enzymes. All cancers invade or metastasize, but each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment, and study.

About 1.2 million new cases of invasive cancer are diagnosed each year in the United States, and about 500,000 people die annually of the disease. Cancer is the second most deadly disease and is expected to surpass heart disease early in the 21st century to top that nefarious list (see Chapter 193). Over the past half century, the frequency of most cancers has been stable, but some dramatic changes have taken place. Steady declines in stomach and uterine cancer have occurred, the latter undoubtedly due to routine cytologic screening for cervical cancer. The cause of the decline in stomach cancer is unclear but may in part relate to increased use of antibiotics and their effect on chronic *Helicobacter pylori* infection. The most striking change has been the increases in lung cancer in both men and women, undoubtedly related to smoking. Other cancers with increasing mortality, particularly in the elderly, include melanoma, non-Hodgkin's lymphoma, and brain tumors. There have been speculations but little firm evidence to explain these changes. The overall mortality, particularly for those younger than age 65, has declined, primarily due to more effective therapy for cancers of fetal and hematopoietic origin that occur in the younger population.

ETIOLOGY AND PREVENTION. A broad array of agents can cause or directly contribute to a sequence of events or sensitize cells in such a way that cancer develops (see Chapter 190). The final common pathway in virtually every instance is a cellular genetic mutation that converts a well-behaved cellular citizen of the body into a destructive renegade that is unresponsive to the ordinary checks and balances of a normal community of cells. Promoters (oncogenes) and suppressors (like the retinoblastoma or *p53* gene) play a central role in many cases (see Chapter 191). Chemicals such as benzene and nitrosamines, physical agents such as gamma and ultraviolet radiation, and biologic agents such as the Epstein-Barr and hepatitis viruses contribute to carcinogenesis under certain circumstances. Evidence exists to link dietary factors to carcinogenesis; although not as clear as one would like, the evidence is strong enough to recommend diets low in fat and high in fiber. A sensible diet is based on grains, vegetables, and fruits, with smaller than the current average proportions of fat. Inherited susceptibilities are becoming more evident and probably play a key role in a significant number of cancers of the breast and colon. Down syndrome and the Li-Fraumeni syndrome are well-known harbingers of a substantial risk for developing cancer.

The single most important carcinogen in the United States and Europe is tobacco (see Chapter 13), because it causes or contributes to the development of about one third of all cancers: primarily lung, esophageal, head and neck, and bladder. Less well appreciated is the contribution tobacco may make to causing breast, colon, and gastric cancer. Tobacco-related cancer is also important because it is preventable by the obvious, inexpensive, and 100% effective means of abstention. Although the total number of smokers in the United States has declined, women smoke more than ever, adolescents continue to view smoking as socially chic, and the number of smokers in Asia and developing countries is growing at an alarming rate.

EARLY DETECTION OF CANCER. When prevention of cancer is not possible because effective means are lacking, early detection is the next best strategy to reduce cancer mortality. As a general rule, the smaller and more confined the tumor, the more likely therapy will result in permanent cure. This approach has been most successful for directly accessible tumors that have an early malignant or premalignant state. Examples include Papanicolaou smears and surgical conization for cancer of the uterine cervix, physical removal of early skin cancer, and colonoscopic removal of colorectal polyps. Physical examination and indirect methods, such as

Table 189-1 ■ SUMMARY OF AMERICAN CANCER SOCIETY RECOMMENDATIONS FOR THE EARLY DETECTION OF CANCER IN ASYMPTOMATIC PEOPLE

	POPULATION		
TEST OR PROCEDURE	Sex	Age	Frequency
Sigmoidoscopy, preferably flexible	M & F	50 and over	Every 3–5 years
Fecal occult blood test	M & F	50 and over	Every year
Digital rectal examination	M & F	40 and over	Every year
Prostate examination*	M	50 and over	Every year
Papanicolaou test	F	All women who are or who have been sexually active, or have reached age 18, should have an annual Papanicolaou test and pelvic examination. After a woman has had three or more consecutive satisfactory normal annual examinations and Papanicolaou tests, screening may be performed less frequently at the discretion of her physician.	
Pelvic examination	F	18–40	Every 1–3 years with Papanicolaou test
		Over 40	Every year
Endometrial tissue sample	F	At menopause, if at high risk†	At menopause and thereafter at the discretion of the physician
Breast self-examination	F	20 and over	Every month
Breast clinical examination	F	20–40	Every 3 years
		Over 40	Every year
Mammography‡	F	40–49	Every 1–2 years
		50 and over	Every year
Health counseling and cancer checkups§	M & F	Over 20	Every 3 years
	M & F	Over 40	Every year

*Annual digital rectal examination and prostate-specific antigen should be performed on men 50 years and older. If either is abnormal, further evaluation should be considered.

†History of infertility, obesity, failure to ovulate, abnormal uterine bleeding, or unopposed estrogen or tamoxifen therapy.

‡Screening mammography should begin by age 40.

§To include examination for cancers of the thyroid, testes, prostate, ovaries, lymph nodes, oral region, and skin.

From Cancer Facts and Figures—1998. Atlanta, American Cancer Society, 1998.

screening mammography for breast cancer and prostate-specific antigen blood tests for prostate cancer, can also be effective at detecting small malignant or premalignant tumors. However, it is not clear that all in situ breast and prostate cancers will become invasive and fatal, so there is some risk of overtreatment, particularly for prostate cancer.

The American Cancer Society (ACS) has recommended a series of cancer screening procedures for asymptomatic individuals (Table 189–1). Not all experts agree on the frequency or age ranges for employing such procedures, but the ACS recommendations are a well-considered and useful guide that, at the very least, indicates the cancers most amenable to clinically useful early detection by conventional techniques. An even more exciting development in this effort has been the emergence of genetic screening and counseling of families at high risk for developing cancer. Individuals at risk are identified largely by analysis of family pedigrees, and the increasing availability of the revolutionary tools of molecular biology can identify specific genetic mutations (see Chapter 191). It is certain that many such genes will be identified, focusing the cancer screening and early detection efforts more efficiently and productively on high-risk populations (see Chapter 190).

CANCER TUMOR GROWTH. Although it is impossible to know the specific details of early in vivo tumor growth and the efficiency of tumor cell renewal of human cancer, clinical and laboratory observations have provided a reasonable conceptual framework. This framework should be used with caution, however, because it is certain that the intrinsic factors that control tumor growth and propagation are far more complex, episodic, and heterogeneous than currently known, even within a single tumor mass. Furthermore, the stromal environment and neovascularization of tumors have become more central to our understanding of this process than heretofore. Nonetheless, the following description can be a useful reference point.

A tumor reaches the size of clinical detectability when it contains about 10^9 cells, weighing about 1 g and occupying a volume of about 1 mL. A three-log increase to 10^{12} cells, 1 kg, and 1000 mL is often lethal. Below 10^9 cells, the tumor is usually undetectable, but it has already undergone at least 30 doublings, and only 10 further doublings will produce the 1 kg of tumor. This exercise illustrates how much has already occurred, with all the opportunities for the cancer to undergo advantageous mutation and metastasis, before clinical detection. Once the tumor has grown into the clinically evident range, it tends to grow progressively slower with increasing size. This deceleration of growth probably occurs because the tumor outgrows its blood supply, reaches anatomic boundaries, and responds to yet undiscovered feedback regulation from other members of the now larger and more heterogeneous mass of tumor cells. Thus, cancers probably grow much like bacteria after inoculation into a favorable medium. The phases of bacterial growth describe a sigmoid curve (Fig. 189–1): an early lag phase of inapparent or slow growth followed by exponential growth. Growth then slows when new cell production and cell death are nearly equal, with the latter phase in culture due to crowding and inadequate nutrients. Of course, in bacteria as well as cancers, the specific growth characteristics differ among types as well as within types that have developed subpopulations of mutant clones.

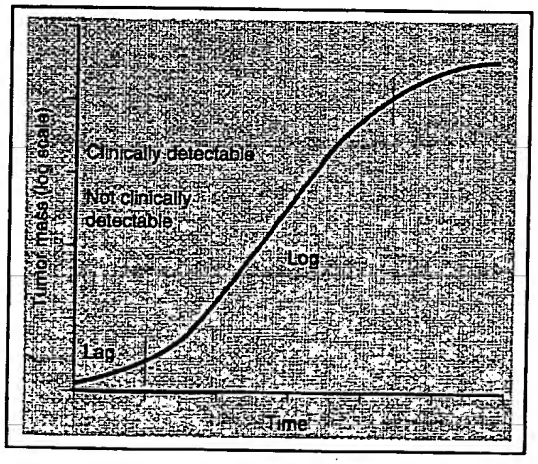

FIGURE 189–1 ■ A schematic representation of the phases of growth of a cancer. After a period of inapparency (lag phase), growth tends to be logarithmic, followed by deceleration due to inadequate nutrients, competitive inhibition among cells, or a lack of neovascularization. (This growth resembles the growth curve of bacteria inoculated into a favorable medium.) The tumor has gone through many doublings before it becomes clinically apparent.

Most chemotherapy acts by damaging DNA, so it tends to be most effective in rapidly growing tumors such as acute leukemia, lymphomas, and testicular cancers. Also, after gross surgical removal, residual cancer cells may grow more rapidly and be more sensitive to subsequent ("adjuvant") chemotherapy. The sensitivity or resistance to chemotherapy or irradiation, however, probably has as much or more to do with the specific biochemical and metabolic features of the cancer cell as with its growth characteristics (see Chapter 198).

MANAGEMENT OF THE PATIENT WITH CANCER

Oncology has been transformed over the past 40 years. From a diverse set of orphan diseases usually managed by surgeons alone and viewed with despair by most physicians, it has become a complex and exciting discipline that draws its strength from the essential partnership of specialists in medicine, surgery, pediatrics, pathology, radiation oncology, diagnostic imaging, psychiatry, and others. This remarkable evolution can be credited to therapeutic successes and biologic advances that could not be imagined in the early 1950s. Oncology has pointed the way to an understanding of the biologic variability of cancer and the success that is possible with a coordinated multimodal approach to therapy.

GOALS. Any physician who seriously and expertly assumes responsibility for the management of patients with cancer should have three sets of goals: therapeutic, human, and scientific. The initial therapeutic goal is to cure patients and return them to a normal place in society. This goal, which should be attempted in virtually all cancers, even when the likelihood of cure is small, requires an attitude of reasonable hope and determination as well as a willingness to attempt difficult, dangerous, and sometimes daring approaches to fundamentally resistant diseases. If, after a reasonable attempt, permanent cure is not possible, the physician must not abandon the patient but rather should aim for a secondary goal—a long, qualitatively satisfactory remission. If and when this second goal is no longer possible, the tertiary level of therapeutic intent is to obtain a remission of any kind and duration; however, at this stage and later, one is less willing to expose the patient to the possibility of serious side effects or long hospitalization. When the possibility of remission of any type becomes remote, the fourth goal is to control the disease and symptoms by the judicious use of palliative therapeutic measures. The objective in this final stage is terminal comfort care, which is always difficult because it requires the admission that specific therapy is no longer of any value. Instead of blood transfusions, antibiotics, or chemotherapeutic agents, the physician must use pain medications, sedation, psychosocial support, and other comfort measures with the thought of returning the patient to the home or another appropriate setting and to the support of family.

The human goals in oncology are inextricably linked with the therapeutic and scientific goals. Physicians, nurses, and other health care providers must be sensitive to the particular needs of the patient and family and understand the social environment from which they came and to which they must return. The physician must help patients maintain their dignity, understand their weaknesses, and refuse to allow any frustration, animosity, or excessive friendship to develop and threaten good judgment and the best interests of the patient.

The use of scientific methods in oncology is only in its adolescence, and definitive treatment has been established for only a small proportion of the circumstances and types of cancers that can arise. Systematic protocol studies yield useful information about a new drug, a novel regimen, or a biologic feature. Presentation and

criticism of each other's efforts in a collegial and scientific manner are essential to advancing the knowledge about a particular treatment. Physicians who manage a small number of patients per year cannot possibly have the background and support necessary to treat these complex diseases adequately. This task is best left to specialists who participate in active scientific programs and have the resources to deliver optimal clinical care. It is also important to understand the limitations of science; at times, the best option is no specific anticancer treatment at all.

DIAGNOSTIC PRINCIPLES. The first diagnostic principle is that adequate tissue must be obtained from the tumor to establish the specific diagnosis and subtype of cancer. The rare exceptions are instances in which a biopsy might be life threatening and the anatomic location is virtually pathognomonic of a specific histology; two notable examples are brain tumors and anterior mediastinal tumors that compress the trachea and blood vessels. In the latter situation, often due to a lymphoma, corticosteroids may reduce the tumor size and relieve symptoms before a biopsy is attempted. More often, an adequate sample must be obtained before therapy is started unless complete surgical excision is definitively diagnostic and therapeutic. Because management of each type and subtype of cancer is often distinctive, every effort must be made to obtain appropriate samples, even if therapy is delayed for a short time. A specific diagnosis is seldom a problem in the leukemias because bone marrow aspiration usually affords a ready answer; solid tumors may present greater difficulty. Cancer diagnosis also requires an understanding of paraneoplastic syndromes (see Chapter 195), endocrine (see Chapter 194) and cutaneous manifestations of cancer (see Chapter 196), and oncologic emergencies (see Chapter 199).

A second diagnostic principle is to establish the extent of the disease. In the leukemias, this goal can be accomplished readily by physical examination, routine laboratory tests, chest roentgenography, and examination of cerebrospinal fluid. With solid tumors, determination of the extent of the disease, that is, the *stage* of the tumor, often involves major surgery and an extensive examination that includes diagnostic imaging. A coordinated approach involving the surgeon and pathologist is crucial to determine the extent of tumor invasion; without this approach, one may lack essential information for planning treatment and for judging its success. Failure to detect a tumor that has extended to regional lymph nodes can lead to undertreatment and a false impression that the local treatment, whether surgery or radiation therapy, was adequate. Generic staging systems (Table 189–2) can be supplemented by detailed and specific staging systems that have been developed for most cancers to recognize peculiar pathogenetic features, modes of spread, and potential curability. In addition, modern oncology demands an extensive biologic classification of leukemias and solid tumors, often requiring sophisticated scientific approaches not available a few years ago: monoclonal antibodies to determine the phenotype of lymphomas and leukemias; light and electron microscopy with special stains to determine the presence of glycogen, enzymes, or other substances that help to classify solid tumors; chromosomal analysis and modern molecular probes that identify unique characteristics of a disease; and responsible oncogenes, suppressor genes, and familial genes (see Chapter 191).

Table 189–2 ■ SIMPLIFIED GENERIC CANCER STAGING SYSTEM

Stage 1	Localized. Usually confined to the organ of origin. Usually curable with locally effective measures such as surgery or irradiation.
Stage 2	Regional. Extends beyond organ of origin but remains nearby, in lymph nodes, for example. Often curable by local measures alone or in combination (surgery ± irradiation) or by a local modality with chemotherapy.
Stage 3	Extensive. Has extended beyond regional site of origin, crossing several tissue planes or extending more distantly via lymphatics or blood. Also may be confined to an organ or region, but be unresectable because of anatomic extent or location. This stage is used rather than stage 2 or stage 4 depending on the usefulness of local and systemic treatment modalities and the likelihood of cure for that specific cancer.
Stage 4	Widely disseminated. Often involves the bone marrow or multiple distant organs. Rarely curable with current armamentarium.

THERAPEUTIC PRINCIPLES. The first step in treatment is to know the patient. All pertinent information—medical, developmental, and social—must be sought before treatment is planned. The second step is to know the tumor: its usual behavior, usual rate of growth, mode of spread, whether it is local or systemic, and any features that may provide prognostic or therapeutic leads. Third, the physician must know the available therapies: not only the therapeutic modalities such as chemotherapy, radiation therapy, and surgery, but also the skills and limitations of colleagues. Finally, the physician must know his or her own skills, experience, objectivity, and limitations. All these factors shape decisions concerning the patient. Caring for patients with cancer is not easy; the physician must be prepared for disappointment as well as success.

Clarity of intent—whether curative, palliative, or supportive—will avoid confusion of approach and method. Treatment protocols, either research or "standard of care" regimens, are important tools that allow strategies to be planned before immediate decisions become necessary. Protocols are also more likely to provide useful conclusions from a study or experience, because a scientific question or a uniform approach has been formulated and data have been collected in a systematic manner. A protocol is, however, only a road map. The planned therapy may require adjustment if complications develop after treatment has begun. Although many of these adjustments can be anticipated and specified in the protocol, not every circumstance can be foreseen. A protocol also is intended to provide practical information that will lead to improved treatment of subsequent patients.

THERAPEUTIC MODALITIES. There are four principal therapeutic modalities for cancer. *Surgery* is the oldest and most definitive when the tumor is localized under the most favorable anatomic circumstances. For example, for a small tumor localized in the breast, the interior of one kidney, or the peripheral edge of the liver, surgery is usually definitive, curative, and leaves no undue side effects. For many solid tumors, however, surgery alone is inadequate because of local or distant spread. Surgery is also crucial in establishing the extent of a tumor. Considerable surgical skill and experience are required to approach a tumor that may or may not be resectable, achieve tumor-free margins, and obtain the necessary tissue without causing further dissemination.

Radiation therapy is most useful for localized tumors that cannot be resected at all or without serious morbidity and for tumors, such as Hodgkin's disease, that tend to spread to predictable contiguous sites. Therefore, a port of radiation can be enlarged beyond the known extent of the tumor and be quite effective. Radiation therapy is also sometimes useful before surgery to reduce tumor size or after surgery to reduce the risk of recurrence. For some cancers, radiation therapy may also be used in combination with chemotherapy. Unfortunately, radiation therapy can have serious side effects (see Chapter 19), especially in children who are growing and developing. The dosage of radiation therapy is based on an estimate of the dose absorbed by tumor, measured in units called centigrays (cGy) or grays (Gy), where 100 cGy = 1 Gy.

Chemotherapy was the first systemic treatment for any cancer. It most often consists of a combination of drugs, which is almost always more effective than the sequential use of single agents. Because tumors develop subpopulations of cells that differ in their sensitivity to antineoplastic drugs, combinations of agents destroy more cells more rapidly, thereby reducing the frequency of emergence of resistant clones. The mechanisms of action differ widely among common chemotherapeutic agents, although DNA damage is the common final pathway. Toxicity also differs among agents; myelosuppression and gastrointestinal disorders are the most common disturbances. Although toxicity is a concern, for many cancers the best therapeutic results depend on the intensity of the dosage; that is, effective agents given at higher doses over a shorter period are more efficacious than less intensive regimens. The physician must straddle the fine line between too much and too little. Chemotherapy is used (1) as a definitive treatment, as in leukemia and some lymphomas; (2) as a principal form of treatment, as in testicular cancer and Ewing's sarcoma; or (3) as an adjuvant to another modality, such as amputation for osteosarcoma or surgical resection for breast or bowel cancer.

Biologic therapy for cancer includes, in addition to bone marrow transplantation, biologic response modifiers such as lymphokines or

198 PRINCIPLES OF CANCER THERAPY

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The development of effective anticancer drugs has progressively integrated medical management with surgery and radiation therapy in the multimodal treatment of cancer. The development of new cytotoxic and endocrine agents and the introduction of biologic therapy based on recombinant synthesis of interferons and cytokines have expanded medical management, as has the treatment of the complications of cancer. The physician also must be familiar with palliative aspects of cancer care, including management of pain (see Chapter 27) and treatment of life-threatening complications (see Chapter 199).

Although current systemic therapy can cure few forms of metastatic cancer, it is now increasingly effective as a component of multimodal management of apparently localized cancers known to have a high frequency of occult micrometastatic spread. This approach is predicated on the availability of specific systemic agents with antitumor activity in advanced cancers of the same histopathology. Not all patients are candidates for attempts at cancer therapy because of limitations in available drugs or co-morbidity from other medical problems. To a significant extent, cancer is a disease of the elderly, and treatment for many types of cancer in patients older than the age of 65 remains difficult because of the reduced host tolerance to the toxicities of many cancer chemotherapeutic agents. Patients and families must be fully informed about the nature of planned treatment, whether curative or palliative in intent. Inasmuch as prognosis for individual patients is currently based on statistical estimates, the physician must evaluate each patient individually in relation to relevant prognostic factors in attempting to develop a treatment plan.

DEVELOPMENT OF A TREATMENT PLAN

The major clinical features of cancer to be considered in developing a treatment plan include (1) specific histologic diagnosis of the neoplasm, (2) tumor burden and extent of specific organ involvement (stage), and (3) biologic characteristics and other prognostic factors relevant to the specific type of cancer.

DIAGNOSIS. Accurate histologic diagnosis and staging critically influence treatment selection. Increasingly, immunohistochemical analysis helps in subtyping lymphomas and distinguishing among various morphologically "undifferentiated" neoplasms (see Chapter 200). Tumors of diverse histogenesis can have markedly different prognosis and treatment. Electron microscopy sometimes can help by identifying specific morphologic features such as melanosomes (in melanoma) or desmosomes (in carcinomas) that permit more specific classification. Other distinctive biologic markers include immunohistochemistry (e.g., overexpression of cyclin D in mantle cell lymphoma), hormone receptor expression, serum or urinary tumor markers (e.g., β-human chorionic gonadotropin, α-fetoprotein, carcinoembryonic antigen, CA-125, myeloma proteins, urinary 5-hydroxyindole acetic acid), karyotype, or molecular analysis. Increasingly, molecular biologic methods for DNA analysis are also playing a role in diagnosis by identifying characteristic gene rearrangements (e.g., Southern blots), gene deletions, or oncogene expression. Cellular proto-oncogene amplification and expression have been linked to the pathogenesis of various neoplasms (see Chapter 191). Recently identified genes regulate the cell cycle and provide "checkpoints" when damage to DNA occurs. Determination of the status of the products of the *p53* and retinoblastoma genes is becoming increasingly important in assessing tumor biology and prognosis, because tumors with mutant or null *p53* and lacking a functional retinoblastoma protein may have a poor prognosis.

In the leukemias and lymphomas, such information can prove important for selecting appropriate treatment approaches. For example, the approach to treatment of T-cell or B-cell lymphomas differs as a function of cell lineage, which often cannot be identified with standard histologic approaches. Specialized studies can in some instances provide evidence for a treatable or curable form of cancer that might otherwise go unrecognized.

STAGING. Assessment of the body burden and spread of cancer by clinical means (staging) is important in developing the treatment plan. Most staging systems assess the size of the primary tumor and define regional lymph node involvement as well as the presence or absence of distant metastatic disease. It is important to distinguish between clinical and pathologic staging and to recognize that pathologic staging employing surgical biopsy is generally more accurate. Increasingly, staging can be accomplished by using non-invasive imaging procedures such as chest radiography and magnetic resonance imaging (MRI) or computed tomography (CT). In the diagnostic evaluation of specific forms of cancer, such as breast or prostate cancer, bone scans can be useful to evaluate advanced disease but have minimal use in early localized disease unless the patient has skeletal symptoms. For multiple myeloma, bone scans are of less use than skeletal radiographs. The temptation to use a variety of redundant and expensive tests such as CT, MRI, and ultrasonography to examine the same site should be avoided. It is important to focus on the benefit-to-risk ratio of invasive procedures such as staging laparotomy. The patient's age, performance status, concomitant medical problems, and histologic diagnosis all must be considered; then the procedure should be performed only if it may influence the treatment plan. For patients who present with life-threatening local complications of cancer (e.g., spinal cord compression, upper airway obstruction, the superior vena cava syndrome, or obstructive jaundice) (see Chapter 199), it is usually necessary first to treat the local complication. Even in these cases, a pathologic diagnosis should be established if at all possible before treatment is started.

OVERALL ASSESSMENT. Once diagnosis and staging have been performed, the information must be integrated into an optimal treatment plan. For patients with apparently localized cancers, multidisciplinary input is important, because a combined-modality approach may be indicated. The biologic characteristics of the specific cancer must be considered. For many tumor types, histopathologic features such as grade of tumor cell differentiation are important, with a less differentiated or undifferentiated phenotype indicating a more aggressive neoplasm. For some sites, other biologic factors are of greater value than histologic grade. For example, in breast cancer, the presence or absence of estrogen or progesterone receptors and the DNA-index and ploidy status as determined by flow cytometry provide useful information in developing a treatment plan. Some patients with a minimal tumor burden (e.g., stage I) of currently incurable B-cell neoplasms (e.g., chronic lymphocytic leukemia [CLL] and multiple myeloma) are best watched expectantly rather than treated. By contrast, almost all patients with diffuse large cell (intermediate- or high-grade) lymphoma should be treated aggressively with curative intent, irrespective of stage, unless they are very elderly and have other major medical problems.

In any given patient, it is important to decide whether curative therapy is available or not, and, if so, whether the patient's age and overall medical condition permit a curative approach. If cure is not an option, one must consider whether palliation with prolongation of survival (and relief of symptoms) can be achieved. For old and infirm patients, a palliative approach may be preferable, particularly if there is significant morbidity associated with the treatment approach under consideration. On the other hand, some forms of cancer therapy are very effective and well tolerated even with advanced age (e.g., use of tamoxifen in adjuvant therapy of postmenopausal breast cancer or of chlorambucil for chronic lymphocytic leukemia). For many tumor types, it is important to examine results of recent prospective clinical trials relevant to the patient's diagnosis and clinical setting and, if possible, to enter patients in clinical trials.

THERAPEUTIC MODALITIES

Three primary therapeutic approaches dominate the treatment of cancer: surgery, radiation therapy, and medical therapy. A fourth modality, biologic therapy (cytokines, antibodies, vaccines), is beginning to add another dimension to treatment programs.

Surgery

Cancer surgery is most useful to establish a tissue diagnosis, to excise the primary tumor with clear surgical margins free of tumor, and to determine the extent of cancer with staging procedures. Surgery is a simple and safe means to remove solid tumors when the tumor is confined to a specific anatomic site of origin. However, in the case of some solid tumors, most patients already have metastatic disease at the time of presentation. In evaluating major surgery for an individual patient, it is important to assess the operative risk-to-benefit ratio for the procedure in the context of the patient's general health status, the extent of the tumor, and the likelihood that it can be completely removed. Additionally, the technical complexity of the surgical procedure, the type of anesthesia needed, and the experience of the personnel must also be considered.

With advances in both radiation and chemotherapy, the need for radical surgery has diminished. However, it remains a major primary approach to curative cancer therapy. For testicular cancer, even in the presence of limited metastatic disease, regional lymphadenectomy after radical orchiectomy can be curative and eliminate the need for chemotherapy in some patients who have metastases only to retroperitoneal lymph nodes. For many other sites, surgical resection of regional lymph nodes is performed for diagnostic rather than therapeutic purposes. For example, in breast cancer, the presence or absence of axillary lymph node involvement is the single most important factor in evaluating the likelihood of distant recurrence, and this information is currently not obtainable by non-surgical means. Similarly, surgical staging of nodal involvement in colorectal cancer plays an important role in deciding whether adjuvant systemic chemotherapy is indicated.

Initial cancer therapy often requires a multimodal approach to maximize the chance of cure while simultaneously reducing the extent of surgery required. Multimodal approaches require close communication among the involved physicians before surgery. Early communication is improved by obtaining histopathologic diagnosis by needle biopsy or local excision of the primary cancer before more extensive therapy. Two examples are of note in this regard: (1) the management of osteogenic sarcoma with limb salvage surgery, irradiation, and adjuvant chemotherapy and (2) the management of early breast cancer with lumpectomy, axillary staging followed by primary irradiation, and adjuvant systemic administration of cytotoxic or endocrine agents. In both instances, the combined approach yields a better cosmetic and functional outcome. Screening mammography can establish a diagnosis of breast cancer when the tumor is less extensive and when likelihood of cure is greater. Improved plastic surgical techniques have also made breast reconstruction possible for women who either require or prefer mastectomy rather than lumpectomy followed by radiation therapy.

In addition to its use in diagnosis, staging, and primary therapy, cancer surgery also plays an important role in the management of some patients with more extensive cancer. In ovarian cancer, when the gynecologic oncologist "debulks" peritoneal and omental spread and leaves the patient with minimal residual disease, patients become better candidates for systemic chemotherapy and have a better survival. Additionally, early resection of pulmonary metastases of soft tissue sarcomas or of solitary brain metastases in melanoma, colon, or breast cancer may provide marked palliation and improved survival, albeit with only occasional cures.

Radiation Therapy

Radiation therapy has made major strides in instrumentation, physics, radiobiology, treatment planning, and applications to curative and palliative cancer therapy. In general, the term *radiation* refers to ionizing radiation that is either electromagnetic or particulate (e.g., x-rays). Compared with surgery, radiation therapy has distinct advantages in the locoregional treatment of cancer. Radiation causes less acute morbidity and can be curative for some specific sites while preserving organ or tissue structure and function. An example is the use of radiation for the curative treatment of early-stage laryngeal cancer wherein vocal function can be preserved.

The basic unit of ionizing irradiation is the gray (Gy), which has superseded the rad (1 Gy = 100 rads = 100 cGy) (see Chapter 19). By interaction with molecular oxygen, radiation induces the formation of superoxide, hydrogen peroxide, or hydroxyl radicals that damage or break cellular DNA, the critical target for radiation-induced cell death. Both single- and double-strand breaks of the DNA helix can be induced, with the latter constituting lethal damage. Single-strand breaks, if not repaired by the cell, can also result in cell death. High linear energy transfer (LET) radiation can induce direct damage to the molecular structure of DNA.

Radiation has limitations in the treatment of bulky tumors. Large tumors frequently have poorly perfused, hypoxic zones in which radiation often fails to induce needed reactive intermediaries. Various forms of irradiation are used for different therapeutic objectives. For example, electron-beam irradiation deposits most of its energy in the skin and soft tissues and can be useful for superficial therapy of skin neoplasms such as mycosis fungoides. Low-energy (kilovoltage) x-rays expend most of their effects on the overlying tissues above a deep-seated tumor and therefore cause considerable normal tissue damage. By contrast, higher-energy x-rays (megavoltage) or x-irradiation from a cobalt-60 source spare the skin, deposit their energy at greater depth, and provide a better approach to treating deep-seated neoplasms. Use of radioactive implants also can be useful in some settings (e.g., cervical cancer, prostate cancer). The use of multiple irradiation fields reduces the dose to normal tissue while increasing the dose to the tumor. The use of fractionated doses causes less cumulative damage to normal tissues than to the tumor, because the normal tissues are often able to repair sublethal damage more quickly. Additionally, as a tumor shrinks with therapy, its oxygenation can improve and render it more radiosensitive. The selection of treatment is based on the relative radiosensitivity of the tumor and of the normal organs and tissues within the radiation field (Table 198–1).

The combined use of multiple fields, fractionated irradiation, and megavoltage radiation equipment is optimized by treatment individualized to the patient's tumor. Although the major uses of radiation therapy involve local irradiation of sites of tumor involvement, total-body irradiation or total lymphoid irradiation is a valuable part of a preparative regimen for allogeneic or autologous bone marrow transplantation for leukemia or lymphoma (see Chapter 182).

Radiation therapy has important palliative applications. One of these is for bone pain due to metastatic involvement of the skeleton. Irradiation can also cause sufficient cytoreduction of tumor in bone to permit healing of osteolytic lesions and thereby prevent pathologic fractures of weight-bearing bones. Other examples include tumor shrinkage to relieve postobstructive infection in lung cancer and to suppress bronchial or gastric bleeding secondary to cancer.

Although modern radiation therapy with megavoltage equipment has proved to be extremely useful, even higher energy radiation approaches are currently in development. These include the use of higher LET sources of irradiation (e.g., neutrons, charged particles, heavy ions), which may also provide selective advantages for specific tumor sites and reduce the need for oxygenation of tumor tissue. Additionally, several classes of compounds are under study as radiosensitizers to enhance the cytotoxic effects of radiation on tumor cells. One class is the halopyrimidines, including bromodeoxyuridine, fluorouracil, and fluorodeoxyuridine, which sensitize

Table 198–1 ■ TOLERANCE OF NORMAL TISSUES TO IRRADIATION

TISSUE	TOXIC EFFECT	LIMITING DOSE (Gy)*
Bone marrow	Aplasia	2.5
Lung	Pneumonitis, fibrosis	15.0
Kidney	Nephrosclerosis	20.0
Liver	Hepatitis	25.0
Spinal cord	Infarction, necrosis	45.0
Intestine	Ulceration, fibrosis	45.0
Heart	Pericarditis, myocarditis	45.0
Brain	Infarction, necrosis	50.0
Skin	Dermatitis, sclerosis	55.0

*Radiation in 2.0-Gy fractions to the whole organ for 5 days weekly produces a 5% incidence of the listed toxicities at the limiting doses listed.

DNA to strand breakage by radiation. Other chemotherapeutic agents, including gemcitabine and taxol, are also under investigation as radiosensitizing agents. Several sulfhydryl compounds (e.g., amifostine) are also under investigation as potential radioprotective agents.

Although the term *radiation* normally refers to ionizing irradiation, several other forms of radiation are also used in cancer treatment. These include hyperthermia and photodynamic therapy, both of which are still undergoing development. Some tumors show thermal sensitivity to temperatures in the range of 41° to 43° C and may be more sensitive than surrounding normal tissues. Hyperthermia appears to work best on bulky tumors with poor blood supply in which the tumor cells are in an acidic environment. A variety of approaches can induce local or regional hyperthermia (e.g., ultrasonography, microwaves, regional perfusion) and may enhance the effects of ionizing irradiation or chemotherapy on local tumors.

Photodynamic therapy (PDT) involves the preliminary systemic administration of a photosensitizing compound such as a hematoporphyrin derivative (e.g., dihematoporphyrin ether, Photofrin II). Such hematoporphyrins are concentrated in the vicinity of local tumors and can be activated with local exposure to visible red light (usually 630 nm), with a resulting preferential toxicity to cancer cells. The intense light used for PDT can be delivered by means of a fiberoptic probe, which can be used for various internal sites as well as on the skin. The mechanism of action of PDT is poorly understood but may involve vascular damage or a direct toxic effect on tumor cells. Side effects of photodynamic therapy include hypersensitivity to light (skin and eyes). Locally, PDT induces transient sunburn and hyperpigmentation as well as local tumor necrosis. Tumor sites amenable to PDT include skin recurrences of breast cancer (e.g., chest wall) and malignant lesions in the endobronchus, peritoneal cavity, and bladder. Photodynamic therapy has not been approved by the U.S. Food and Drug Administration (FDA) and remains investigational.

Medical Therapy

Curative therapy has been developed for a series of relatively uncommon disseminated neoplasms, and useful palliative therapy has been developed for some common forms of cancer (Table 198–2). With rare exceptions, effective therapy has used combinations of anticancer drugs. Increasingly, anticancer drugs are used in concert with surgery and/or irradiation.

Ideally, anticancer drugs should eradicate cancer without harming normal tissues; however, this goal has not been achieved, and most useful drugs have significant side effects. The introduction of anticancer drugs for clinical use has largely been predicted from animal tumor models. Perhaps because the initial murine models were for acute leukemia, many of the developed drugs are general antiproliferative agents. Accordingly, they are more effective against rapidly proliferating tumors than against some of the more slowly growing solid tumors and are more toxic to rapidly growing tumors than to normal host tissues. Nevertheless, such generally antiproliferative agents can have important toxic side effects on normal tissues that divide rapidly, such as bone marrow, gastrointestinal mucosa, and skin.

Table 198–2 ■ RESPONSIVENESS OF CANCER TO CHEMOTHERAPY

Cure (>30%) of Advanced Disease
Choriocarcinoma
Acute lymphocytic leukemia (childhood)
Malignant lymphoma (Hodgkin's disease, diffuse high-grade or intermediate-grade non-Hodgkin's lymphoma)
Hairy cell leukemia
Testicular cancer
Childhood solid tumors (embryonal rhabdomyosarcoma, Ewing's sarcoma, Wilms' tumor)
Acute myelocytic leukemia
Acute lymphocytic leukemia (adult)
Promyelocytic leukemia
Significant Palliation, Some Cures of Advanced Disease (5–30%)
Ovarian cancer
Bladder cancer
Small cell lung cancer
Gastric cancer
Palliation, Probably Increases Survival
Breast cancer
Multiple myeloma
Head and neck cancer
Adjuvant Treatment Leading to Increased Cure
Breast cancer
Colon cancer
Osteogenic sarcoma
Early-stage large cell lymphoma

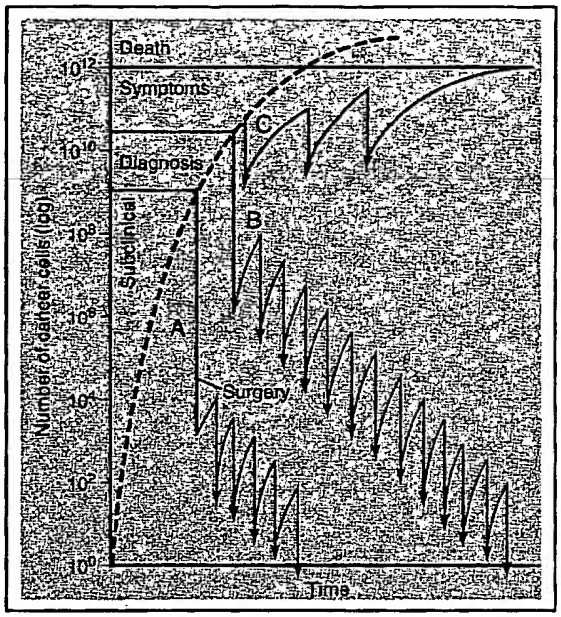

FIGURE 198–1 ■ The relationship of tumor growth and tumor burden to treatment strategies and outcome with systemic chemotherapy. Human tumors grow in accord with the Gompertz curve (dashed line), with a decreasing doubling time as tumor burden increases. Treatment interventions relate to tumor type and extent of disease. A, Surgery followed by pulse courses of adjuvant chemotherapy. B, Systemic chemotherapy for stage III Hodgkin's disease. C, Palliative chemotherapy for advanced non–small cell cancer. In A, combined modality has curative potential with the addition of chemotherapy after surgery. Cure is also possible in B with prolonged administration of combination chemotherapy. In C, the patient's tumor burden is too great and the potency of the drugs for this specific form of cancer is inadequate because of development of drug resistance. (Modified from Salmon SE, Sartorelli AC: Cancer chemotherapy. *In* Katzung BG [ed]: Basic and Clinical Pharmacology, 4th ed. Norwalk, CT, Appleton & Lange, 1989, p 685.)

CELL KINETICS AND RESPONSE TO CHEMOTHERAPY. A number of related factors, including total tumor burden, cell kinetics, and intrinsic sensitivity, influence the response to anticancer drugs. In both animal models and human tumors, growth occurs in accord with gompertzian kinetics. Initially, growth occurs rapidly, and most tumor cells traverse the complete cell cycle. As the tumor burden grows larger, the rate of tumor cell doubling progressively slows (Fig. 198–1), and the fraction of cells traversing the cell cycle decreases as more and more cells remain "hung up" in a G_0 phase. Whereas the population doubling time may be in the range of 1 to 2 days at the subclinical phase (with less than 1 g of tumor), by the time the tumor burden has reached 1 kg or more, the tumor cell population doubling time may be 3 to 6 months. A significant problem in the treatment of high tumor burden metastatic solid tumors is that the tumor exhibits a significant degree of heterogeneity; subpopulations of cells exhibit differing biologic, kinetic, antigenic, and drug-sensitivity profiles.

Several important features related to cell kinetics and tumor burden are important with respect to drug dose, scheduling, and response to chemotherapy. Anticancer drugs can be classified as either cell cycle specific (CCS) or cell cycle non-specific (CCNS) (Table 198–3). CCNS agents have greater effects on cycling than on non-cycling cells but nonetheless can exert anticancer effects on non-cycling cells, whereas CCS agents do not. Endocrine agents

Table 198–3 ■ RELATIONSHIP OF TUMOR CELL CYCLE TO ACTIVITY OF MAJOR CLASSES OF CYTOTOXIC ANTICANCER DRUGS

CELL CYCLE–SPECIFIC (CCS) AGENTS	CELL CYCLE–NON-SPECIFIC (CCNS) AGENTS
Antimetabolites (cytarabine, fluorouracil, methotrexate, mercaptopurine, hydroxyurea)	Alkylating agents (busulfan, cyclophosphamide, mechlorethamine, melphalan, thiotepa, chlorambucil)
Anthracyclines (doxorubicin, daunorubicin)	Antibiotics (dactinomycin, mitomycin)
Bleomycin	Platinum compounds (cisplatin, carboplatin)
Camptothecins (irinotecan, topotecan)	Nitrosoureas (BCNU, CCNU)
Plant alkaloids (vincristine, vinblastine, etoposide, taxol)	Dacarbazine
	L-Asparaginase

are also in a sense cycle active, because they block the transition of tumor cells from G_1 to the S phase of the cell cycle. However, certain endocrine agents (e.g., tamoxifen, progestins) are considered to suppress growth rather than kill tumor cells. Endocrine agents are therefore often given for many years, whereas cytotoxic agents are usually given over a time course measured in months.

An important concept in cancer chemotherapy is that cellular killing with cytotoxic agents follows first-order kinetics, with a given dose of drug killing only a fraction of the tumor cells. This "fractional kill hypothesis" is particularly relevant to CCNS agents and predicts that the greater the dose of drug administered, the greater the "log kill" of tumor cells that will occur.

The concept of combination chemotherapy was developed to take advantage of the fact that many anticancer agents have differing mechanisms of action and side effects. This concept was based on the hypothesis that giving drugs with differing mechanisms of action may achieve synergistic antitumor effects while simultaneously retarding the rate of development of drug resistance. Additionally, by careful selection of drugs in a combination to include those with known single-agent activity against the tumor and different normal tissue toxicities, the side effects would be "spread" across different tissues and organs. The validity of this concept has been borne out clinically. Optimal results for most tumor types sensitive to chemotherapy have been achieved with drug combinations, often employing CCNS and CCS agents possessing different mechanisms of action. For example, cisplatin has demonstrated clear-cut synergy with etoposide in testicular cancer and small cell lung cancer and with fluorouracil in both head and neck and esophageal cancer. The major potential toxicity for cisplatin is nephrotoxicity, whereas myelosuppression is the major side effect for both etoposide and fluorouracil.

New drugs entering clinical trials are normally first tested in patients with a large tumor burden of metastatic cancer who have relapsed from known effective chemotherapy regimens. Although this approach is ethically most acceptable, it nonetheless represents a significant obstacle to new drug development, because these patients have a lower probability of response to a new drug than those with a lower tumor burden or those who have not been previously treated. The presence of the blood-brain barrier has been a major obstacle to the development of chemotherapy for primary or metastatic tumors in the brain. At present, brain tumors are treated chiefly with surgery and radiation therapy.

DRUG RESISTANCE. For many of the drug-responsive tumor types (see Table 198–2), major cytoreduction occurs with initial chemotherapy. Some months to years thereafter, however, tumor regrowth occurs and continues even though the same drugs are reinstituted. This observation usually reflects the acquisition of drug resistance by the tumor to the specific drugs. Most drug resistance is considered to result from the high spontaneous mutation rate of cancer cells, which leads to the development of heterogeneous subpopulations, some of which exhibit resistance to various drugs. Perhaps the most important form of resistance is multidrug resistance (MDR), mediated by a cell membrane glycoprotein (the P-glycoprotein), which is thought to function as an energy-dependent efflux pump that actively extrudes a variety of cytotoxic agents from the cell (Fig. 198–2).

Drugs pumped out of the cancer cell by the P-glycoprotein include natural products such as plant alkaloids (vincas, podophyllotoxins, taxol), antibiotics (dactinomycin, doxorubicin, daunorubicin), and some synthetic agents (e.g., mitoxantrone). The P-glycoprotein is normally expressed in tissues such as the gut and the kidney, perhaps to deal with toxic products in the environment. Cancer cells with mutations to "switch on" the expression of the gene responsible for encoding the P-glycoprotein show resistance to a wide variety of useful anticancer drugs. Techniques such as immunohistochemistry, Western blots, and Northern blots can be used to detect the presence of P-glycoprotein in tumor tissues. Clinical studies suggest that patients whose tumors express P-glycoprotein have a poor prognosis. Culture studies performed on biopsy specimens in vitro have documented that P-glycoprotein–positive tumors usually exhibit resistance to doxorubicin. Tumor types such as sarcoma, neuroblastoma, malignant lymphoma, and myeloma are usually P-glycoprotein negative at the time of diagnosis but are frequently positive for P-glycoprotein when the patient relapses from chemotherapy. A series of non-cytotoxic drugs has been identified to reverse drug resistance mediated by P-glycoprotein (e.g., verapamil, cyclosporine). In drug-resistant patients with malignant lymphoma and multiple myeloma, high doses of verapamil given simultaneously with vincristine and doxorubicin can reverse resistance to these agents, with some patients regaining remission. Although verapamil is not an ideal chemosensitizer (because of its cardiovascular side effects), other potential chemosensitizers are now being tested in an effort to identify more effective and less toxic chemosensitizers. In the long run, such chemosensitizers may find their major use to prevent development of MDR expression. Other mechanisms of multidrug resistance include an increase in proteins called MRP and LRP, and mutations in topoisomerase II, which is the target for the anthracycline drugs and for etoposide.

Drug-specific resistance mechanisms also occur (Table 198–4). For example, intrinsic or natural resistance of patients with acute

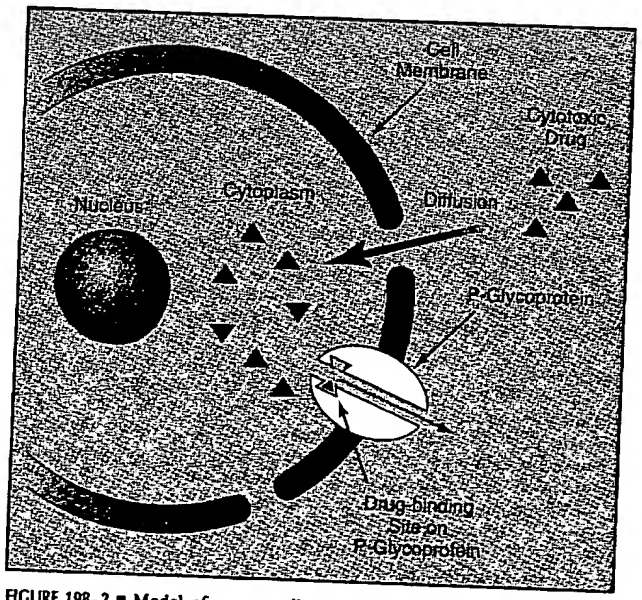

FIGURE 198–2 ■ Model of cancer cell expressing P-glycoprotein. This transmembrane protein is believed to function as an energy-dependent efflux pump or drug transporter. It has acceptor sites to which various natural product anticancer drugs bind, after which they are pumped out of the cell. Chemosensitizers such as verapamil also bind to the drug acceptor sites on P-glycoprotein and can competitively inhibit its function.

Table 198-4 ■ SOME MECHANISMS OF RESISTANCE TO CHEMOTHERAPY DRUGS

DRUG	MECHANISMS OF RESISTANCE
Methotrexate	Impaired transport or amplification of dihydrofolate reductase
Cytarabine	Decreased deoxycytidine kinase or increase in cytidine deaminase
5-Fluorouracil	Increase in thymidylate synthase
Cisplatin	Decreased uptake Increase in repair enzymes
Taxol, *Vinca* alkaloids	MDR expression Mutations in tubulin (decreased binding)
Doxorubicin	MDR expression Decrease or alterations in topoisomerase II
Irinotecan, topotecan	Decrease in topoisomerase I

myelogenous leukemia to methotrexate is attributed to lack of retention of this drug by leukemic blasts. These cells form low levels of methotrexate polyglutamates, the drug species that are retained by cells. In contrast, acute lymphocytic leukemia blasts (pre-B, not T cells) convert methotrexate to its polyglutamates efficiently and are sensitive to treatment with this drug. Acquired resistance, fortunately now noted in the minority of patients with this disease treated with combination chemotherapy, has been found to be associated with impaired uptake due to abnormalities in the reduced folate carrier transport protein, or to low-level amplification of the dihydrofolate reductase gene, whose product is the target for methotrexate.

PREDICTIVE TESTING IN VITRO. Many approaches have been developed to assess the probability of relapse after primary therapy or response to a given type or class of endocrine or cytotoxic agents. The "S-phase" fraction of the tumor cell population undergoing DNA synthesis as well as DNA ploidy can be determined by flow cytometry. For several tumor types, patients with a high percentage of tumor cells in DNA synthesis and/or hyperdiploidy have a high likelihood of relapsing early after local primary cancer therapy. Taken with other prognostic characteristics, such flow cytometry assays may aid in identifying patients who should receive adjuvant chemotherapy. This approach is currently being applied to patients with stage I breast cancer in an effort to decide which patients are at higher risk for recurrence.

Diagnostic laboratories can provide the results of S-phase and DNA ploidy analysis as well as the findings from estrogen and progesterone receptor testing. Estrogen and progesterone receptor assays in breast cancer are used primarily to identify patients likely to respond to endocrine agents in either the adjuvant or recurrent disease setting. The sex steroid hormone receptors are located in the cell nucleus and must bind the hormone and translocate it to cellular DNA to exert endocrine action through gene activation or suppression. Additionally, in the absence of adjuvant therapy, tumors that are estrogen or progesterone receptor positive take longer to recur and have a better overall prognosis than tumors that are receptor negative. Studies have shown that another tumor cell constituent, the *HER-2/neu* oncogene, can be of prognostic value (see Chapter 258). Amplification of the number of copies of the *HER-2/neu* gene or increased expression of the gene product by RNA or protein analysis appears to predict a poor prognosis in both breast and ovarian cancer. The protein product of *HER-2/neu* is expressed on the surface of tumor cells and structurally appears to be a hormone receptor analogous to the epidermal growth factor (EGF) receptor. An antibody to this receptor can cause tumor regression in patients whose breast cancers overexpress this protein. Abnormalities in expression of *p53*, the tumor suppressor gene, have been associated with a worse prognosis when present in a wide variety of solid tumors. Studies indicate that the lack of wild type *p53* protects cells from chemotherapy-induced apoptosis. Lack of the retinoblastoma protein may also decrease the sensitivity of tumor cells to antimetabolites. Thus, measurement of abnormalities of these tumor suppressor genes in tumors may be an additional prognostic factor in treatment outcome.

Chemosensitivity assays appear to predict drug resistance but are somewhat less accurate for predicting which drugs will be useful for an individual patient. Another type of testing for drug resistance that is now being applied to fresh frozen (and in some instances to fixed) tissues is immunohistochemical testing for P-glycoprotein expression.

Knowledge of the mechanism of action of certain drugs has been used to predict sensitivity to these agents. For example, fresh sarcoma cells in short-term mixture have been shown to be useful for evaluating potential anticancer effects of various folate analogues as measured by inhibitors of thymidylate synthesis in a whole-cell assay. In addition, the low levels of thymidylate synthase mRNA expression in tumors has also correlated well with response to fluorouracil treatment among patients with gastric or colon cancer, and studies are in progress to determine if this assay may be used to select patients for treatment with this drug.

PHARMACOKINETIC CONSIDERATIONS. Although intrinsic drug sensitivity appears to be the most critical determinant of response to chemotherapy, pharmacokinetic factors related to the route of administration, bioavailability, metabolism, and elimination are probably of greater importance in cancer therapy. Many cytotoxic agents have a steep dose-response curve and a resulting narrow therapeutic index. Thus, at too low an available dose level within the tumor, no response is seen. On the other hand, at higher doses, host toxicity supervenes and is usually dose limiting. Because of the steep dose-response relationship, doses of most cytotoxic agents are calculated in relation to body surface area, a more accurate approach than dose calculations based on body weight. Patients usually prefer the oral route of drug administration, but marked variations in bioavailability among oral formulations plus inconsistent patient compliance tend to limit such an approach. For example, with the alkylating agent melphalan, more than a 10-fold variation in plasma levels has been documented after standard dosing. Unfortunately, plasma assays are not routinely available for most anticancer drugs, and the only semiquantitative indicator of bioavailability of cytotoxic agents is the occurrence of myelosuppression after drug administration. For patients presenting with hypercalcemia or other complications of myeloma, oral melphalan therefore seems undesirable, because such patients need to achieve effective plasma levels immediately. Similar difficulties are faced with oral administration of fluorouracil, methotrexate, and 6-mercaptopurine. Bioavailability is adequate after oral administration of agents such as tamoxifen and cyclophosphamide.

The intravenous route of drug administration is preferable for most cytotoxic anticancer drugs, because it ensures adequate plasma levels while minimizing compliance problems. For some agents, continuous intravenous drug administration for 4 days or longer provides better results and less toxicity than do bolus or short-duration infusions because tumor response for many agents can be related to the "area under the plasma disappearance curve (AUC)" for the drug, whereas toxicity generally relates more directly to peak plasma concentrations than to the AUC. With the advent of vascular access devices such as subcutaneous ports, external catheters, and infusion pumps, outpatient continuous infusion chemotherapy can now be used for stable drugs such as fluorinated pyrimidines, anthracyclines, and *Vinca* alkaloids. Subcutaneous administration can be used effectively with drugs such as cytarabine, interferon-α, and erythropoietin. Subcutaneous dosing provides more sustained plasma levels than can be obtained with intravenous administration. Depot intramuscular formulations are available for a variety of endocrine agents used in treatment of breast or prostate cancer.

Regional administration of chemotherapy can be effective for several tumor sites. For metastatic colon cancer limited to the liver, hepatic artery catheterization for arterial infusion of 5-fluorodeoxyuridine or 5-fluorouracil can be used effectively by connection of the catheter to an external pump or to an implantable perfusion pump. In either instance, arterial infusions are often administered for 14 days, followed by a similar rest period. A relatively high objective response rate of metastatic colon cancer in the liver can be obtained by this means, but this route is ineffective for metastases outside the liver. Hepatic artery chemotherapy is expensive and associated with complications, including arterial thrombosis, biliary sclerosis, and chemical hepatitis. Nonetheless, it can induce sustained remissions for a year or more in selected patients. Regional infusion or isolated perfusion has been used with melanomas and sarcomas of the lower extremity. With melanoma metastases of the lower extremity, melphalan or cisplatin has been administered in this fashion with or without regional hyperthermia.

Intraperitoneal drug administration has also gained increasing popularity and appears to show particular promise for patients with peritoneal carcinomatosis, where it can induce remissions of established metastatic disease. In ovarian cancer, intraperitoneal chemotherapy is being studied as a follow-up to cytoreductive surgery. Diffusion of intraperitoneally administered drugs is limited to a few millimeters of tumor tissue. Accordingly, intraperitoneal chemotherapy is seldom warranted in patients with bulky tumor masses. For optimal distribution, the drug is usually diluted in 2 L of parenteral fluid for injection. Preferred drugs for intraperitoneal administration are those that tend to be limited largely to the peritoneal cavity, have good properties for tumor penetration, and produce little or no local toxicity. Mitoxantrone, fluorodeoxyuridine, and cisplatin have these favorable characteristics and can be quite useful. With each of these drugs, the intraperitoneal concentration can be 1000-fold higher than measured in the systemic circulation. Other agents sometimes used in intraperitoneal administration include thiotepa, fluorouracil, and methotrexate. Intraperitoneal drug administration can be performed at repeated intervals with relative ease if a surgically implanted Tenkoff catheter is connected to a subcutaneous port. Mild to moderate chemical peritonitis and the development of peritoneal adhesions are common complications of intraperitoneal chemotherapy and limit repeated use. Intracavitary drug administration with instillation of a biologic agent such as bacille Calmette-Guérin (BCG) or interferon or a variety of cytotoxic agents (e.g., thiotepa, doxorubicin, mitomycin, cisplatin) is used to treat superficial bladder cancer.

The intrathecal route can be used to deliver therapy to the meninges. Methotrexate, cytarabine, and thiotepa can be given by this route to prevent meningeal leukemia and treat central nervous system leukemia or lymphoma or meningeal carcinomatosis. Intrathecal methotrexate has been used effectively for acute lymphoblastic leukemia as an adjuvant to initial systemic chemotherapy and has reduced the frequency of central nervous system relapse in patients in complete peripheral remission.

EVALUATION OF RESPONSE. Objective measurement of tumor shrinkage with medical or radiation therapy has prognostic importance. Reduction of symptoms alone does not indicate a response. Cure or significant prolongation of survival occurs in patients who achieve complete response (disappearance of all evidence of cancer). Whenever possible, confirmation of response should be obtained pathologically through the use of restaging procedures. Many patients achieve only a partial response, defined as a reduction of tumor burden by 50% or greater. Patients achieving partial responses generally have palliation of symptoms and usually have a prolonged period without tumor growth. Modest improvements in survival accompany some partial responses.

Tumor markers in the blood or urine can be useful in monitoring response to therapy (see Chapter 192). Patients with testicular germ cell tumors and gestational choriocarcinoma cannot be considered potentially cured unless the titer of marker substance falls below the limit of detection. Tumor marker studies are also useful in judging responses in ovarian cancer, prostatic carcinoma, colon cancer, multiple myeloma, neuroblastoma, and the carcinoid syndrome.

Response to adjuvant chemotherapy cannot be evaluated by these methods, because insufficient tumor usually remains to employ physical or imaging studies or tumor markers. However, in the neoadjuvant setting in which chemotherapy is used before local surgery, the response to chemotherapy provides an "in vivo sensitivity test" to determine whether the employed agents can provide effective therapy after surgery.

CYTOTOXIC ANTICANCER DRUGS. Safe and effective cytotoxic cancer chemotherapy requires considerable understanding of the pharmacology and toxicology of these drugs. Drug doses are cited for single-agent chemotherapy; when drugs are used in combinations (Table 198–5), lower doses may be required for some agents. Therefore, it is wise to use effective and well-established combination protocols with known side-effect profiles rather than to improvise combinations. The development of new combinations of standard drugs is best done in the research setting.

ALKYLATING AGENTS. The major clinically useful alkylating agents (Table 198–6) kill cells by binding to and cross-linking DNA through a bis(chloroethyl)amine, ethyleneimine, or nitrosourea moiety. Although these agents likely kill cells by alkylating DNA (primarily at the N7 position of guanine), they also react chemically with nucleophilic molecules (e.g., sulfhydryl, amino, hydroxyl, and phosphate groups). Alkylating agents differ in the severity of early and late side effects. The major acute side effects are gastrointestinal (nausea and vomiting) and hematologic (myelosuppression). Most alkylating agents cause local skin and subcutaneous tissue necrosis when infiltrated into the skin.

All alkylating agents can potentially induce ovarian or testicular failure as well as acute leukemia. Agents such as melphalan and chlorambucil appear to be more leukemogenic than cyclophosphamide, whereas busulfan and the nitrosoureas cause more persistent damage to hematopoietic stem cells and more prolonged myelosuppression.

Cyclophosphamide and Ifosfamide. Cyclophosphamide (Cytoxan) is the most widely used alkylating agent and is effective in the treatment of both hematologic malignancies and solid tumors. It does not have significant vesicant effects, because it is a prodrug that requires bioactivation in the liver. Metabolism of cyclophosphamide by cytochrome P-450 produces the active metabolite phosphoramide mustard plus acrolein. Cyclophosphamide is available in both intravenous and oral formulations and is well absorbed by the oral route. A commonly used single-agent dosage schedule for intravenous cyclophosphamide is 1.0 g/m^2 every 3 weeks. Cyclophosphamide produces a less severe pattern of myelosuppressive toxicity than other alkylating agents; it can cause severe neutropenia but usually of relatively short duration, and thrombocytopenia is less severe than with other alkylators. Other toxicities of cyclophosphamide include alopecia and immunosuppression. When high doses are used (e.g., for bone marrow transplantation), cyclophosphamide can also cause myocardial necrosis or the syndrome of inappropriate secretion of antidiuretic hormone. Although cyclophosphamide can cause acute non-lymphocytic leukemia and pulmonary fibrosis, these toxicities are more common with other alkylating agents. Both cyclophosphamide and a related analogue, ifosfamide (Ifex), can cause hemorrhagic cystitis. Bladder toxicity can be blocked by administration of the uroprotective agent mesna (Mesnex), which is concentrated in the urine and inactivates the toxic metabolite acrolein. Mesna is particularly valuable with ifosfamide, which otherwise routinely causes bladder toxicity. Ifosfamide causes somewhat less hematologic toxicity than other alkylating agents and at present is used mostly for second-line therapy (e.g.,

Table 198–5 ■ COMMON COMBINATION CHEMOTHERAPY REGIMENS

ABBREVIATION	DRUGS EMPLOYED	INDICATION
MOPP	Nitrogen mustard (Mustargen), vincristine (Oncovin), prednisone, procarbazine	Hodgkin's disease
ABVD	Doxorubicin (Adriamycin), bleomycin, vinblastine, dacarbazine	Hodgkin's disease
CHOP	Cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), prednisone	Non-Hodgkin's lymphomas
CMF	Cyclophosphamide, methotrexate, 5-fluorouracil	Breast cancer
CAF	Cyclophosphamide, doxorubicin (Adriamycin), 5-fluorouracil	Breast cancer
M-VAC	Methotrexate, vinblastine, doxorubicin (Adriamycin), cisplatin	Bladder cancer
PVB	cisplatin, vinblastine, bleomycin	Testicular cancer
VAD	Vincristine, doxorubicin (Adriamycin), dexamethasone	Multiple myeloma

Table 198–6 ■ ALKYLATING ANTICANCER DRUGS

DRUG	MAJOR INDICATIONS
Nitrogen mustard	Hodgkin's disease
Melphalan	Multiple myeloma
Chlorambucil	Chronic lymphocytic leukemia
Busulfan	Chronic myelocytic leukemia
Cyclophosphamide	Lymphoma, breast cancer, bladder cancer
Ifosfamide	Soft tissue sarcoma, lymphoma
Nitrosoureas (carmustine, lomustine)	Brain tumors, lymphoma
Procarbazine	Hodgkin's disease
Dacarbazine	Melanoma, Hodgkin's disease
Cisplatin, carboplatin	Testicular, ovarian cancer, head and neck, lung cancer

for therapy for testicular cancer, lymphoma, or metastatic sarcomas).

Chlorambucil. Chlorambucil (Leukeran) has antitumor activity similar to that of cyclophosphamide and is also well absorbed after oral administration. It is used primarily in the treatment of chronic lymphocytic leukemia, low-grade lymphomas, macroglobulinemia, and polycythemia vera. Chlorambucil does not cause hemorrhagic cystitis or alopecia, and its gastrointestinal side effects are mild. However, it is myelosuppressive. Acute non-lymphocytic leukemia has been reported in patients treated with chlorambucil for polycythemia vera or other disorders.

Melphalan. Melphalan (Alkeran) is L-phenylalanine mustard and gains access to cells through an amino acid transport system. Melphalan is commonly given orally in a dosage of 10 mg/m²/day for 4 days every 3 to 4 weeks. Some patients do not absorb the drug; generally, the only clue, other than drug levels, is the absence of myelosuppression. If myelosuppression does not occur, melphalan dosage should be increased in subsequent courses until moderate myelosuppression is induced. Melphalan is commonly used in the treatment of multiple myeloma and ovarian cancer and occasionally for other tumor types. The drug induces acute non-lymphocytic leukemia in some patients treated for myeloma or ovarian cancer.

Busulfan. Busulfan (Myleran) is a methane-sulfonate–based alkylating agent that has specificity for myeloid neoplasms and appears to have less antitumor activity in other forms of cancer. It is available only for oral administration and is used primarily for treatment of chronic myeloid leukemia (CML) or as part of marrow ablative regimens followed by stem cell transplantation. Busulfan can produce protracted myelosuppression, and hematologic recovery should be complete before the next course is administered. Busulfan can also cause pulmonary fibrosis, hyperpigmentation, weakness, and wasting. Adrenal function remains normal.

Nitrosoureas. Carmustine (BCNU) and lomustine (CCNU) are rapidly biotransformed through non-enzymatic hydrolysis to release intermediates with alkylating and carbamoylating activities. Carmustine is available for intravenous use, and lomustine is given orally. The major toxicity of nitrosoureas at standard dosage levels is on hematopoietic stem cells; delayed, prolonged myelosuppression can result. At high doses (e.g., in preparative regimens for bone marrow transplantation), nitrosoureas can induce a chemical hepatitis or pneumonitis. Prolonged use with total doses greater than 1500 mg/m² can also result in pulmonary fibrosis or renal failure. Because of their high lipid solubility and ability to cross the blood-brain barrier, the nitrosoureas have some activity against primary brain tumors. The nitrosoureas also are useful in the management of Hodgkin's disease and multiple myeloma and as part of combined-modality therapy for cancers of the anal canal.

Platinum Compounds. Cisplatin and carboplatin are platinum-coordination compounds with broad-spectrum antitumor activity and synergistic interactions with a variety of other cytotoxic agents, including alkylating agents, antimetabolites, and natural products. Although their mechanism of action is not completely understood, they act similarly to alkylating agents in terms of their ability to bind to the N7 position of guanine and crosslink DNA. However, cross-linking with adenine and cytosine also occurs, as does binding to RNA and protein.

Cisplatin and carboplatin differ in their toxicity profiles. Both drugs are administered intravenously. Cisplatin is commonly given in a dose of 100 mg/m² every 3 weeks, whereas the dose of carboplatin is in the range of 450 mg/m² at similar intervals, although larger doses may be tolerated. After intravenous infusion, the major acute toxicity for both cisplatin and carboplatin is nausea and vomiting, which is worse with cisplatin. Satisfactory suppression of the gastrointestinal side effects of platinum compounds requires potent antiemetic agents, often in combination. Large cumulative doses of cisplatin also cause renal toxicity, which can be largely prevented if the patient is well hydrated with simultaneous saline infusions and diuretics. Large cumulative doses can also cause a progressive neuropathy. Myelosuppression is minimal with cisplatin but is dose limiting with carboplatin. Although carboplatin is less toxic than cisplatin, its efficacy is equivalent for some, but not all, tumors. The lack of myelosuppression favors cisplatin for use in some drug combinations with myelosuppressive agents. A new platinum analogue, oxaloplatin, may have activity against colon cancer comparable with that of fluorouracil.

ANTIMETABOLITES. The antimetabolites (Table 198–7) are structural analogues of normal biochemical compounds, most of which are involved in DNA or RNA synthesis and generally function as CCS agents. Antimetabolites are classed in relation to their mechanisms of action.

Pyrimidine Antagonists. *Cytarabine (Cytosine Arabinoside, Cytosar-U, Ara-C).* Cytarabine is an S-phase–specific agent that is particularly useful in acute non-lymphocytic leukemia and, to a lesser extent, in other hematologic malignancies. Its active form, ara-CTP, competitively inhibits DNA polymerase, blocking DNA synthesis. Ara-C also blocks chain elongation and ligation of fragments into newly synthesized DNA. Ara-C is given intravenously and crosses the blood-brain barrier. It is administered either by continuous infusion or in bolus doses by the intravenous or subcutaneous route for 5 to 7 days. In an alternative schedule that exceeds the manufacturer's recommended maximum, high-dose ara-C is administered in doses of 1 to 3 g every 12 hours for 3 to 5 days and yields higher response rates. The duration of intracellular retention of ara-CTP appears to predict ara-C antileukemic effects, with best results in patients who have the longest ara-CTP retention times. Both standard and high-dose ara-C can produce severe myelosuppression. With the high-dose regimen, chemical conjunctivitis is common and can be ameliorated with corticosteroid ophthalmic drops. With rare exception, complete remissions can be achieved in acute leukemia only if ara-C is administered with sufficient intensity to drive the bone marrow to severe hypocellularity and destroy the leukemic blast population. Thereafter, the marrow is repopulated by residual normal progenitors that were suppressed by the leukemia. Ara-C is generally used in combination with daunorubicin in the treatment of acute non-lymphocytic leukemia but also acts synergistically with other drugs, including cisplatin. Cytarabine can also be given intrathecally in doses of 75 to 100 mg as treatment for leukemic or carcinomatous meningitis.

Gemcitabine. Gemcitabine (Gemzar), is a novel nucleoside analogue with structural similarities to cytarabine. Both drugs are metabolized by cytidine deaminase and require intracellular phos-

Table 198–7 ■ ANTIMETABOLITE ANTICANCER DRUGS

DRUG	MAJOR INDICATIONS
Folic acid antagonists (methotrexate)	Acute lymphocytic leukemia, choriocarcinoma, breast cancer, bladder cancer, head and neck cancer, lymphoma
5-fluorouracil	Gastrointestinal cancer, breast cancer, cancer of the head and neck
5-fluorodeoxyuridine	Regional therapy (intra-arterial or intraperitoneal) for colon cancer metastasis
Cytarabine	Acute leukemia
Gemcitabine	Cancer of the pancreas
6-Mercaptopurine, 6-thioguanine	Acute leukemia
Fludarabine	Chronic lymphocytic leukemia, low-grade lymphoma
2-Chlorodeoxyadenosine	Hairy cell leukemia, low-grade lymphoma
Deoxycoformycin	Hairy cell leukemia, T-cell lymphoma
Hydroxyurea	Chronic myelocytic leukemia

phorylation for activation. The drug is approved for use in the treatment of patients with advanced pancreatic carcinoma. Gemcitabine significantly improves disease related symptoms in approximately 25% of patients, and a modest increase in survival was demonstrated in patients with pancreatic carcinoma when compared with treatment with 5-fluorouracil. The drug is well tolerated; reversible myelosuppression is the dose-limiting toxicity. The drug is administered intravenously over 30 minutes, weekly for 3 weeks followed by 1 week of rest.

Fluorouracil and Floxuridine. Fluorouracil (5-FU) is an important anticancer agent used to treat a variety of solid tumors, including cancers of the head and neck, esophagus, breast, and colon. It acts synergistically with a variety of agents, including platinum compounds and radiation therapy. Studies indicate that "pulse" or bolus injections of 5-FU are cytotoxic mainly as a result of incorporation into RNA, whereas continuous infusions of this drug (2 or more days) kill cells by inhibiting DNA synthesis and producing "thymine-less death." 5-FU is usually given intravenously by bolus or infusion schedules but can also be used in intra-arterial, intracavitary, and topical therapy. An optimal schedule for 5-FU administration is a 5-day continuous infusion at a dose rate of 1.0 g/m²/day. This schedule causes some gastrointestinal toxicity but only a mild degree of myelosuppression. Full doses of cisplatin can be administered additionally, providing an active treatment program in the neoadjuvant chemotherapy of head and neck and esophageal cancer. 5-FU administered on a weekly intravenous bolus schedule produces greater hematologic toxicity and mucositis than lower total doses. Less common toxicities observed with 5-FU include a neurologic syndrome associated with ataxia, chemical conjunctivitis, and a syndrome including chest pain and cardiac enzyme elevation consistent with myocardial ischemia. The bioavailability of 5-FU after oral administration is erratic, and the drug is metabolized mostly during its first pass through the liver.

Both the gastrointestinal toxicity and the antitumor activity of 5-FU can be enhanced by administration of leucovorin, which increases the binding of fluorodeoxyuridine phosphate to thymidylate synthase. This combination appears to increase the antitumor activity of 5-FU in breast and colon cancer. Interferon-α and levamisole also appear to enhance 5-FU activity in colorectal cancer. Levamisole potentiation has been observed only in the adjuvant setting. Recent studies showed that 6 months of treatment with 5-FU and leucovorin in the adjuvant setting is the regimen of choice for patients with colorectal cancer. Both 5-FU and floxuridine (5-FUDR) can be given by hepatic artery infusion to treat patients with colorectal carcinoma with metastases confined to the liver. With the use of a surgically placed vascular access catheter, outpatient hepatic artery infusions can be administered using either an internal or a portable external pump. A limitation is that either 5-FU or 5-FUDR can induce a chemical hepatitis and biliary sclerosis with jaundice. Hepatic dysfunction can be most readily detected by obtaining liver chemistries on day 14 when 5-FU is to be discontinued. Studies indicate that the response rate and duration of remission are increased by the addition of leucovorin (folinic acid) or dexamethasone to 5-FUDR.

Purine Antagonists. *6-Mercaptopurine and 6-Thioguanine.* In contrast to 6-mercaptopurine (6-MP), some 6-thioguanine (6-TG) metabolites are incorporated into both DNA and RNA. 6-TG has some uses in acute non-lymphocytic leukemia in combination with cytarabine, whereas 6-MP is used primarily in acute lymphoblastic leukemia, particularly in childhood. Absorption of 6-MP is variable, but plasma monitoring can identify poor absorbers who have a high likelihood of developing recurrent leukemia, presumably because of inadequate bioavailability of 6-MP. The 6-MP analogue azathioprine is a useful immunosuppressive agent. Because both 6-MP and azathioprine are catabolized by xanthine oxidase, patients must have their thiopurine doses reduced to 25% of their standard doses if they are also receiving the xanthine oxidase inhibitor allopurinol. 6-TG is not catabolized by xanthine oxidase, and dose correction is not required for allopurinol.

Fludarabine. Fludarabine (Fludara, 5-fluoroadenosine monophosphate) is an analogue of adenine that inhibits DNA polymerase and ribonucleotide reductase. Fludarabine is the single most active agent available in the treatment of chronic lymphocytic leukemia and also exhibits some antitumor activity in other indolent lymphomas and macroglobulinemia. Fludarabine is often given intravenously in a dose of 25 mg/m²/day over 30 minutes for 5 days every 4 weeks. The major toxicity is myelosuppression. Higher doses administered in early trials in patients with acute non-lymphocytic leukemia occasionally produced cortical blindness. In the lower-dosage schedule used in chronic lymphocytic leukemia and other lymphoid neoplasms, side effects are usually mild and reversible.

Additional purine antagonists include deoxycoformycin (DCF) and 2-chlorodeoxyadenosine (2-CDA). Both DCF and 2-CDA are extremely active agents in the treatment of hairy cell leukemia and can produce prolonged remissions after a single course of treatment. Both agents also exhibit some antitumor activity in other low-grade lymphoid neoplasms (e.g., CLL and low-grade lymphomas).

Folic Acid Antagonists. Methotrexate (MTX) is a structural analogue of folic acid and is currently the only FDA-approved member of this group. Clinical trials of new antifolates are targeting not only dihydrofolate reductase (e.g., trimetrexate) but also other folate-requiring enzymes such as thymidylate synthase (e.g., raltitrexed). MTX can be administered orally, intramuscularly, or intravenously and is useful primarily as a component of chemotherapy combinations for various types of cancer, including acute lymphoblastic leukemia, small cell lung cancer, bladder cancer, head and neck cancer, and breast cancer. When used in high dosage with leucovorin rescue, it exerts antitumor activity in osteogenic sarcoma. Intracellular formation of polyglutamated forms of MTX is important to the action of MTX, because the polyglutamated forms have equivalent ability to inhibit dihydrofolate reductase action but have a longer intracellular retention time than MTX. The polyglutamates also inhibit other folate-dependent enzymes, including thymidylate synthase. Given satisfactory renal function and adequate hydration, MTX is excreted unchanged mainly in the urine within 12 hours of administration.

Major toxicities of MTX are to rapidly dividing tissues, including the bone marrow, gastrointestinal mucosa, and, to a lesser extent, skin. At high dosages or in patients with impaired renal function, MTX also can induce renal toxicity. Chronic extended use of MTX (e.g., for maintenance treatment of patients with acute lymphocytic leukemia or long-term treatment of patients with psoriasis), occasionally leads to liver fibrosis and cirrhosis. The toxic effects on the rapidly dividing tissues can be circumvented by administering the reduced folate leucovorin (folinic acid) within 36 hours after MTX administration. Leucovorin rescue also can be used when MTX is intentionally administered in higher than manufacturer's recommended maximum dose (e.g., 1500 mg/m² or more). When high-dose MTX is administered, leucovorin must be administered 24 to 36 hours after MTX in dosages of 15 to 50 mg/m² every 6 hours for 48 hours, with the duration of rescue contingent on the serum MTX level. Increased leucovorin dosage and longer periods of rescue are needed in patients with impaired renal function. The high-dose MTX/leucovorin rescue regimen therefore requires good renal function.

NATURAL PRODUCT ANTICANCER DRUGS. The two main classes of natural antitumor products are plant alkaloids and antibiotics (Table 198–8). Resistance to the natural products, with the exception of bleomycin, can be mediated by the P-glycoprotein multidrug resistance mechanism.

PLANT ALKALOIDS. Vincristine and Vinblastine. The *Vinca* alkaloids were isolated from the common periwinkle (*Vinca rosacea*). The major Vinca alkaloids in clinical use, vincristine (Oncovin) and vinblastine (Velban), precipitate tubulin and disrupt cellular microtubules. Whereas the primary toxicity of vinblastine is hematopoietic, vincristine's major toxicity affects peripheral nerves, resulting in sensorimotor and autonomic neuropathies. Common symptoms are paresthesias ("pins and needles sensation") in the digits and progressive muscular weakness with areflexia, particularly in the lower extremities. Footdrop can develop, as can occasional cranial, bladder, or bowel neuropathies. The neurotoxicity subsides slowly after the drug is discontinued, with improvement requiring months, especially if motor function is impaired. The lack of bone marrow toxicity of vincristine has made it useful for combination chemotherapy regimens. The *Vinca* alkaloids have vesicant effects and can be administered only intravenously. Both provide antitumor activity in leukemias and lymphomas as well as in selected solid tumors, including small cell lung cancer and breast cancer. Vincristine is used in various drug combinations, in-

Table 198–8 ■ NATURAL PRODUCT ANTICANCER DRUGS

DRUGS	MAJOR INDICATIONS
Plant Alkaloids	
Vincristine	Lymphoid malignancies
Vinblastine	Hodgkin's disease, testicular cancer
Vinorelbine	Small cell lung cancer
Podophyllotoxins	
Etoposide (VP-16)	Small cell lung cancer, lymphoma
Teniposide (VM-26)	Acute lymphocytic leukemia
Paclitaxel (Taxol)	Ovarian cancer, breast cancer
CPT-11	Colon cancer
Antibiotics	
Anthracyclines	
Doxorubicin	Lymphoma, breast cancer, sarcomas
Daunorubicin	Acute leukemia
Idarubicin	Acute leukemia
Mitoxantrone (synthetic)	Acute leukemia, lymphoma
Mitomycin	Gastrointestinal malignancies
Dactinomycin	Choriocarcinoma, Wilms' tumor, Ewing's sarcoma, rhabdomyosarcoma
Bleomycin	Lymphoma, head and neck cancer
Miscellaneous Agents	
Hexamethylmelamine	Ovarian cancer
Asparaginase	Acute lymphocytic leukemia

cluding MOPP, CHOP, MACOP-B, and M-BACOD for the treatment of lymphomas (see Chapter 179), and VMCP and VAD in the treatment of multiple myeloma (see Chapter 181). Vinblastine's greatest use has been in its incorporation into the PVB regimen for the treatment of non-seminomatous testicular cancers (see Chapter 247), and in the ABVD regimen to treat Hodgkin's disease (see Chapter 180). Vinblastine is also used in combination with cisplatin in non–small cell lung cancer and with mitomycin in metastatic breast cancer.

Vinorelbine. Vinorelbine (Navelbine) is a semisynthetic *Vinca* alkaloid approved for use in the treatment of non–small cell lung cancer. Its spectrum of antitumor activity and its mechanism of action are similar to those of vinblastine and vincristine. In humans, its limiting toxicity, like that of vinblastine is hematologic, and its spectrum of activity and use in combinations is under investigation.

PODOPHYLLOTOXINS. Etoposide. Etoposide (VP-16, VePesid), a semisynthetic glucoside, is produced from extracts of the root of the mayapple or mandrake (*Podophyllum peltatum*). A closely related analogue, teniposide (VM-26), has not been approved in the United States by the FDA. Mechanistically, podophyllotoxins are thought to act as inhibitors of nuclear topoisomerase II, leading to DNA strand breaks. Additional effects include inhibition of nucleoside transport and mitochondrial electron transport. Etoposide is highly lipid soluble and water insoluble and requires a special formulation for intravenous administration. An oral formulation is also available. Good tissue distribution is achieved in all sites other than the brain. A commonly used schedule administers etoposide intravenously for 3 days at a dosage of 150 to 200 mg/m²/day. Etoposide is excreted primarily in the urine and to a lesser extent in the bile. Its dosage should be reduced by half in patients with impaired renal function. The main side effect is myelosuppression, although gastrointestinal toxicity and alopecia also can occur. Etoposide is used primarily to treat metastatic testicular cancer in combination with cisplatin and bleomycin. The combination substitutes etoposide for vinblastine, yielding a less toxic but equally effective regimen. Etoposide also exerts potent effects against small cell lung cancer, lymphomas, and monocytic leukemia.

Paclitaxel. The taxoids are an important new class of anticancer agents that appear to stabilize tubulin as their major mechanism of action. Paclitaxel (Taxol) has been approved for use in the United States for the treatment of breast cancer and ovarian cancer and is also widely used for other epithelial tumors (head and neck, esophagus, non–small cell lung cancer) in combination therapy regimens. For example, the combination of cisplatin and paclitaxel is now first line treatment with a 10 to 20% cure rate for patients with ovarian cancer, where it improves survival compared with cisplatin and cyclophosphamide. The drug may cause hypersensitivity reactions (e.g., hypotension, dyspnea, bronchospasm and urticaria). Typically, premedications are administered before paclitaxel administration to prevent these reactions: dexamethasone, 20 mg orally or intravenously, 12 and 6 hours before treatment; diphenhydramine, 50 mg, 30 minutes before treatment; and an H_2 antagonist (e.g., cimetidine), 300 mg, intravenously, 30 minutes before treatment. Other toxicities include neutropenia, which is dose limiting, myalgias, and peripheral neuropathy, the latter which generally occurs only after multiple courses at conventional doses (135 to 250 mg/m² over 24 hours). Other dosage schedules (3-hour, 96-hour) are under investigation.

Docetaxel. Docetaxel (Taxotere) is a semisynthetic analogue of paclitaxel and has been approved for use in the treatment of locally advanced or metastatic breast cancer that has progressed during anthracycline-based therapy. This drug also has anticancer activity in patients with non–small cell lung cancer. The recommended dose is 60 to 100 mg/m² intravenously every 3 weeks.

ANTITUMOR ANTIBIOTICS. Doxorubicin, Daunorubicin, and Idarubicin. These anthracycline antibiotics were isolated from a variant of *Streptomyces peucetius* and are extremely useful in cancer chemotherapy. Daunorubicin (daunomycin) was the first agent in this class and is active in the treatment of acute leukemia. Its congener, doxorubicin (Adriamycin), has a broader spectrum of antitumor activity, including both hematologic malignancies and a variety of solid tumors such as carcinoma of the breast and thyroid, lymphoma, and myeloma, as well as osteogenic and soft tissue sarcomas. Daunorubicin is frequently used in combination with cytarabine in the treatment of acute myelocytic leukemia, whereas doxorubicin is incorporated into regimens for solid tumors along with cyclophosphamide, fluorouracil, etoposide, vincristine, or cisplatin. Mechanistically, the anthracyclines intercalate with high affinity into DNA and inhibit the action of topoisomerase II, resulting in DNA strand breaks. Anthracycline cardiac toxicity may also be related in part to the generation of free radicals. Both doxorubicin and daunorubicin must be administered intravenously by either bolus injection or prolonged infusion. Extravasation can lead to severe tissue injury. Immediate topical application of 1.5 mL of 99% dimethylsulfoxide (DMSO) has been reported to prevent subsequent ulceration. For prolonged anthracycline infusions, use of a vascular access catheter is advisable. Ulceration and necrosis after anthracycline extravasation usually require surgical débridement of the damaged tissues plus skin grafting.

The most common acute toxicities of the anthracyclines include alopecia, nausea, vomiting, mucositis, and myelosuppression. A dose-dependent, delayed, and potentially irreversible cardiomyopathy with reduced cardiac contractility can develop in patients who receive large cumulative doses of doxorubicin or daunorubicin (see Chapter 64). Acute cardiac arrhythmias are uncommon.

Periodic monitoring for cardiac effects of anthracyclines is normally initiated when a patient has received a total doxorubicin dose of 350 to 400 mg/m². Endomyocardial biopsy can also be used. Cardiac toxicity is uncommon with cumulative bolus doses of doxorubicin of less than 550 mg/m², above which the incidence rises progressively. Elderly patients and others with risk factors for cardiac disease (e.g., hypertension) are at somewhat higher risk for anthracycline cardiomyopathy. Anthracyclines are not recommended for patients who have major pre-existing heart disease. When doxorubicin is administered by continuous infusion (e.g., for 4 to 5 days), there is less cardiotoxicity, and a significantly larger cumulative dose in the range of 1000 mg/m² can usually be administered. However, regular cardiac monitoring is required, and doxorubicin should be discontinued if the left ventricular ejection fraction falls by 15 percentage points and to below 50%. Idarubicin is another anthracycline recently approved for use in the treatment of acute myelocytic leukemia. In controlled studies, idarubicin in combination with cytarabine induced higher remission rates than daunorubicin and cytarabine.

An agent that protects the heart from anthracycline toxicity, dexrazoxane, has been approved for use by the FDA for patients who are treated with cumulative doses of doxorubicin greater than 300 mg/m². Liposomal preparations of doxorubicin are also being evaluated as potentially less cardiotoxic formulations. Toxicities associated with dexrazoxane are pain at the injection site and modest neutropenia and thrombocytopenia. The possibility that dexrazoxane may have an adverse effect on tumor response led to the FDA rec-

ommendation that treatment with this drug should be initiated only when the cumulative dose of 300 mg/m² of doxorubicin was reached.

Bleomycin. Bleomycin (Blenoxane) comprises 11 closely related glycopeptide moieties produced by *Streptomyces verticillus*. The major components are bleomycins A2 and B2. Bleomycin action involves its binding to DNA and generation of superoxide and other reactive oxygen species, including hydroxyl radicals. DNA fragmentation appears to result from the oxidation of a DNA-bleomycin-Fe^{2+} complex. Bleomycin's antitumor activity is schedule dependent, acting primarily at the G_2 phase of the cell cycle. It can be administered by subcutaneous, intramuscular, and intravenous routes. Its major uses are in combination therapy to treat carcinoma of the testis and squamous cell carcinomas of the head and neck, cervix, skin, penis, and rectum. It is also used in combination regimens for treatment of lymphomas (ABVD).

Bleomycin has minimal myelosuppressive effects and is useful in combination with drugs that cause leukopenia. Acute toxicities include anaphylactoid reactions and fever associated with hypotension and dehydration. Patients who have not received bleomycin previously should receive a test dose (e.g., 1 to 2 mg) to discover such adverse reactions. Individual therapeutic doses of bleomycin are usually in the range of 5 to 10 units/m².

The most serious chronic reaction to bleomycin is pulmonary fibrosis related to the cumulative dose of drug and manifested by cough, dyspnea, and bilateral basilar infiltrates on chest radiography. It is possible to screen for earlier pulmonary abnormalities such as a decline in the diffusion capacity, which is usually detectable at total doses of bleomycin above 250 units. If the pulmonary diffusion capacity falls abnormally, bleomycin should be discontinued. The incidence of pulmonary fibrosis rises at total doses above 450 units and is higher in patients with pre-existing pulmonary disease, after lung irradiation, and in the elderly. This toxicity may be irreversible, although corticosteroids may be of some use. Other reactions to bleomycin include skin toxicity with blistering, desquamation, hyperkeratosis of the palms, and hyperpigmentation of creases.

Mitomycin. Mitomycin (Mutamycin, Mitocin-C, Mitomycin C) is isolated from *Streptomyces caespitosus*. Its structure includes quinone, carbamate, and aziridine groups, which may contribute to its antitumor activity. Mitomycin functions as a CCNS alkylating agent after it has been activated in various tissues by the cytochrome P-450 system. Thereafter, it can alkylate DNA to form intrastrand and interstrand crosslinks resulting in cell death. Mitomycin has "bioreductive" properties, with increased cytotoxic effects on poorly oxygenated tumor cells in solid tumors, and has been used in combination with irradiation to treat patients with cancer of the head and neck. Mitomycin's clinical spectrum of antitumor activity includes breast, lung, gastrointestinal, genitourinary, and gynecologic cancers. Mitomycin has been incorporated into a variety of cytotoxic drug combinations for systemic administration, often as second-line therapy for patients who relapse from initial chemotherapy. It is usually administered intravenously but can be used for intravesical therapy of superficial bladder cancer. Its normal intravenous dosage range is 10 to 15 mg/m².

The major toxicity of mitomycin is delayed myelosuppression, usually appearing 4 to 6 weeks after injection. Mitomycin has a cumulative effect on bone marrow stem cells, which can lead to protracted marrow hypoplasia for 3 to 6 months after discontinuing the drug. Nausea, vomiting, and anorexia often occur at the time of administration but can usually be managed effectively with antiemetic agents. Occasionally, mitomycin can induce interstitial pneumonitis, nephrotoxicity, or hemolytic-uremic syndrome.

Dactinomycin. Dactinomycin (Actinomycin D, Cosmegen) was the first effective antitumor antibiotic isolated from *Streptomyces*. It binds to the DNA helix by intercalation between adjacent guanine-cytosine base pairs; it inhibits DNA-dependent RNA synthesis and leads to cessation of most protein synthesis in sensitive cells. The drug is administered intravenously, and its major toxicity is myelosuppression, usually appearing 7 to 10 days after injection. Dactinomycin also causes significant gastrointestinal toxicity with abdominal cramps and diarrhea as well as mucositis. The drug also can cause a radiation "recall" reaction in which cutaneous erythema redevelops at a site of prior irradiation. The principal use of dactinomycin is in pediatric oncology in combination chemotherapy for the treatment of Wilms' tumor, Ewing's sarcoma, and embryonal rhabdomyosarcoma. It has some utility in adults in third-line therapy of germ cell tumors of the testis or ovary, gestational choriocarcinoma, and soft tissue sarcomas.

TOPOISOMERASE I INHIBITORS. This class of drugs binds to topoisomerase I. Two inhibitors of this enzyme have now been approved for clinical use: irinotecan and topotecan.

Irinotecan. Irinotecan (CPT-11, Camptosar) is a prodrug that is rapidly hydrolyzed in vivo to SN-38, a potent inhibitor of topoisomerase I. It has been approved for use in the treatment of patients with colorectal cancer. The dose schedule used most commonly is a single infusion (200 mg/m²) every 3 weeks, although other dose schedules are being explored. The principal dose-limiting toxicities are non-hematologic, in particular diarrhea. Diarrhea may be seen within the first 24 hours of treatment, or later, occurring 4 to 8 days after treatment. Aggressive treatment with loperamide or octreotide at the first sign of diarrhea has allowed patients to tolerate this drug. Severe neutropenia may also occur with CPT-11. Current studies are evaluating combinations of this drug with fluorouracil or raltitrexed (Tomudex), an investigational drug that targets the enzyme thymidylate synthase.

Topotecan. Topotecan (Hycamtin) is approved for use in previously treated patients with ovarian cancer. Its mechanism of action is similar to that of irinotecan, namely, inhibition of topoisomerase I. Topotecan also has activity in other tumors, including hematologic malignancies, small cell lung cancer, neuroblastoma, and rhabdomyosarcoma. The recommended dose is 1.5 mg/m²/day infused intravenously over 30 minutes for 5 consecutive days, every 3 weeks. The dose limiting and most common toxicity is myelosuppression, especially neutropenia.

MISCELLANEOUS ANTICANCER AGENTS. PROCARBAZINE. Procarbazine (Matulane) is an orally administered methylhydrazine derivative that has antitumor activity in Hodgkin's disease (as part of MOPP combination chemotherapy) and in non-Hodgkin's lymphomas, lung cancer, and brain tumors. Procarbazine is usually given in a dose of 100 mg/m²/day for 10 to 14 days in each chemotherapy cycle. Procarbazine is activated metabolically to produce a methyldiazonium ion that binds to nucleic acids, proteins, and phospholipids to inhibit macromolecular synthesis. Its mechanism of cytotoxicity is thought to involve DNA strand scission, possibly through generation of H_2O_2. Procarbazine's principal toxicities are nausea, vomiting, and myelosuppression. One of procarbazine's metabolites is a monoamine oxidase (MAO) inhibitor that can cause toxicity when the patient is taking other MAO inhibitors. Patients taking procarbazine may develop hypertension if they ingest tyramine-rich foods such as ripe cheese, wine, and bananas. Disulfiram-like reactions are also seen, with sweating and headache after alcohol ingestion. Other infrequent reactions include hemolytic anemia and pulmonary reactions. Procarbazine is also known to be leukemogenic, carcinogenic, and mutagenic and is considered to play a significant role in the development of late leukemias and other second malignancies in patients with Hodgkin's disease. Procarbazine also produces azoospermia and anovulation. Because alternative combinations lacking procarbazine can be used in the treatment of Hodgkin's disease (e.g., ABVD), the benefits versus risks of using this agent must be carefully considered.

DACARBAZINE. Dacarbazine (DTIC, dimethylimidazole carboxamide) is activated by oxidative *N*-demethylation. A methyl carbonium ion metabolite is thought to be the cytotoxic intermediate with alkylating activity. Dacarbazine is administered intravenously either in a single-day infusion schedule of 750 mg/m² or in fractionated bolus doses over 5 days or more. DTIC causes severe nausea and vomiting, and potent antiemetic agents are required. Myelosuppression is relatively mild. Dacarbazine is used in combination chemotherapy for Hodgkin's disease (ABVD), for soft tissue sarcomas in combination with doxorubicin and other agents, and in single-agent chemotherapy for metastatic melanoma.

HEXAMETHYLMELAMINE (HMM). This agent is available only in an oral formulation because of its sparing solubility. Oral bioavailability of HMM is quite variable, however, and nausea and vomiting can be dose limiting. The gastrointestinal distress increases with daily use, limiting the length of treatment courses (at doses of up to 12 mg/kg/day) to 2 to 3 weeks. Mild myelosuppression occurs. Additionally, HMM can induce both central and peripheral neurotoxicities, including altered mood, hallucinations, and peripheral

neuropathy. HMM is thought to act as an alkylating agent, possibly through the enzymatic hydroxylation of its demethyl metabolites to cytotoxic methylol compounds. HMM exhibits antitumor activity in alkylating agent-resistant ovarian cancer and, to a lesser extent, in several other neoplasms (lung, breast cancer, lymphomas).

HYDROXYUREA. Hydroxyurea (Hydrea, HU) acts as an inhibitor of ribonucleotide reductase, resulting in intracellular depletion of deoxynucleoside triphosphates and inhibition of DNA synthesis. It is available for clinical use in oral formulation. HU's major toxicity is to the bone marrow, and it causes transient dose-related myelosuppression. At high dosage, a megaloblastic anemia can develop, which is non-responsive to vitamin B_{12} or folic acid. Gastrointestinal side effects of nausea and vomiting are also common with high-dose therapy. HU is used primarily to treat chronic myeloid leukemia and polycythemia vera, but it also has some use in head and neck cancer and metastatic melanoma and as a radiosensitizer.

MITOXANTRONE. Mitoxantrone (Novantrone) is an anthracenedione with a structure that appears analogous to that of the anthracyclines. It has been approved by the FDA as a second-line agent for treatment of acute leukemia in relapse but is also useful in the treatment of breast cancer and lymphoma. Mitoxantrone binds to DNA and causes strand breaks and inhibits DNA and RNA synthesis. In terms of cellular response by tumor cells, there is not complete cross-reactivity between mitoxantrone and the anthracyclines. Mitoxantrone dosage for acute leukemia is higher than for solid tumors. Comparative studies in patients with advanced breast cancer suggest that it is less active and less toxic than doxorubicin. Its major acute toxicity is myelosuppression. Gastrointestinal side effects, including nausea, vomiting, and mucositis as well as alopecia, are less severe than with the anthracyclines. Mitoxantrone can cause some cardiac toxicities, usually manifest by development of arrhythmia at the time of injection, and can exacerbate pre-existing anthracycline-induced cardiomyopathy. It can be used intraperitoneally in patients with ovarian cancer, because most of the drug remains in the peritoneal cavity. This approach reduces systemic toxicity, but it can induce chemical peritonitis and adhesions.

ASPARAGINASE. L-Asparaginase (Crasnitin, Elspar) is a bacterial enzyme isolated from *Escherichia coli* or *Erwinia carotovora*. Its major use is to treat lymphoblastic leukemias and some lymphomas with a deficiency in asparagine synthetase and cellular dependence on exogenous asparagine. L-Asparagine is a non-essential amino acid, and most normal cells can synthesize their required asparagine. Therapeutically, L-asparaginase depletes the plasma of asparagine by converting it to aspartic acid and ammonia. Most patients develop fever and chills as well as nausea and vomiting after administration, but these symptoms can usually be reduced or prevented by premedication with antiemetics and anti-inflammatory agents. Asparaginase toxicity can produce abnormal liver function tests (aspartate aminotransferase T, alkaline phosphatase, and bilirubin) as well as hypoalbuminemia and reductions in plasma levels of clotting factors and insulin. Other occasional toxicities include pancreatitis and central nervous system abnormalities, which can lead to confusion or coma. Repeated use of asparaginase leads to the development of antibodies that can inhibit its activity and accelerate its clearance as well as induce hypersensitivity reactions. Patients developing hypersensitivity after asparaginase administration may exhibit hypotension, laryngeal edema, bronchospasm, and urticaria. Switching to an asparaginase derived from a different bacterial species can bypass neutralizing antibodies in hypersensitive patients. The lack of myelosuppressive or gastrointestinal toxicity has facilitated incorporation of L-asparaginase into drug combinations for the treatment of acute lymphocytic leukemia (ALL). A useful combination in ALL is methotrexate, followed 24 hours later by L-asparaginase.

MANAGEMENT OF TOXICITY

Most cytotoxic drugs are also toxic for host cells, and treatment schedules must take this into account.

DOSE ADJUSTMENTS FOR BONE MARROW TOXICITY. Doses of myelosuppressive agents often must be adjusted downward to avoid serious or life-threatening side effects such as granulocytopenic fever and thrombocytopenic bleeding. For most drugs, empirical schedules have been developed for drug administration with single agents or combinations of myelosuppressive drugs normally given every 3 to 4 weeks. The interval between treatments provides time for hematopoietic recovery of normal myeloid progenitors in the bone marrow and avoids cumulative myelosuppression. It is essential to check the patient's white blood cell count, differential, and platelet count immediately before each course of myelosuppressive chemotherapy. During the first few cycles of chemotherapy, and at intervals thereafter, it is useful to check counts between treatment courses, particularly to determine the nadir of absolute granulocyte count (AGC). Falls of AGC below 1000/μL increase the risk of infection; AGCs below 500/μL represent a potentially fatal risk. Because hematopoietic recovery can occur rapidly after the nadir, the AGC immediately before the next course can be normal even though the nadir count may have been very low. For some drug combinations with low but brief AGC nadirs, prophylactic antibiotic agents (e.g., ciprofloxacin, sulfamethoxazole-trimethoprim) that will bracket the AGC nadir can protect against infection secondary to neutropenia. In general, if the AGC immediately before the next course of chemotherapy is less than 2000/μL, the dose of myelosuppressive drugs should be reduced by 50%. With an AGC of less than 1500/μL, doses should be reduced by 75%. If less than 1000/μL, the drug should be withheld until hematologic recovery occurs. An additional approach to problems of myelosuppression involves the use of bone marrow growth factors, as discussed below under Biologic Agents.

DOSE ADJUSTMENTS FOR IMPAIRED HEPATIC OR RENAL FUNCTION. It is important to make downward dosage adjustments for specific drugs when altered hepatic or renal function plays a major role in drug metabolism. The metabolism of doxorubicin depends on good hepatobiliary function. Patients with a serum bilirubin value of greater than 3.0 mg/dL should have their doxorubicin dose reduced by at least 50% until drug tolerance is established.

Cisplatin, methotrexate, etoposide, hydroxyurea, and bleomycin all are cleared predominantly through renal excretion. Doses of these agents should be decreased approximately in proportion to the decline in renal function as determined by creatinine clearance and reflected by the serum creatinine value.

ENDOCRINE AGENTS

Cancer cells often exhibit susceptibility to hormonal control mechanisms that regulate growth of the normal organ or tissue from which the neoplasm arose. Endocrine therapy (Table 198–9) appears generally to work through cytostatic rather than cytotoxic mechanisms and usually requires long-term suppression. Endocrine therapy includes the use of both hormones and "antihormones," which are either antagonists or partial agonists for a given endocrine mechanism. Inasmuch as the effects of hormones are receptor mediated, evaluation of receptors capable of binding hormones has played an important role in assessing both tumor types and individual patients for possible endocrine therapy.

STEROID HORMONES AND ANTIHORMONES. Cancers arising from endocrine organs and the immune system are susceptible to the effects of steroid hormones, steroid hormone antagonists, and hormone deprivation. The sex steroids and their antagonists represent major agents for the treatment of common cancers arising from the breast, prostate gland, and uterus. The role of endocrine ablation procedures (hypophysectomy, adrenalectomy, oophorectomy, orchiectomy) has diminished as systemic agents have been identified to replace surgical procedures. Nonetheless, oophorectomy and orchiectomy are still useful in the treatment of endocrine-sensitive cancers of the breast and prostate, respectively.

ESTROGENS AND ANTIESTROGENS. Pharmacologic doses of estrogen have therapeutic effects in cancers of the prostate and the breast. Orchiectomy is equally efficacious and lacks feminizing side effects. No evidence suggests an additive effect of the two.

The antiestrogen tamoxifen (Nolvadex) improves survival of postmenopausal women with estrogen and/or progesterone receptor-positive breast cancer in both the adjuvant and metastatic settings. Recent but still controversial studies also suggest that tamoxifen may be a useful adjuvant for hormone receptor–negative cancers in postmenopausal women. A recent breast cancer prevention